*Systematic Review*

# Relationship between the Pre-ECMO and ECMO Time and Survival of Severe COVID-19 Patients: A Systematic Review and Meta-Analysis

Ziqi Tan, Longxiang Su, Xiangyu Chen, Huaiwu He and Yun Long *

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China; b2023001122@pumc.edu.cn (Z.T.); sulongxiang@vip.163.com (L.S.); pumc_2022chenxiangyu@student.pumc.edu.cn (X.C.); tjmuhhw@126.com (H.H.)
* Correspondence: ly_icu@aliyun.com

**Abstract:** Background: Coronavirus disease 2019 (COVID-19) is the etiology of acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation (ECMO) is used to support gas exchange in patients who have failed conventional mechanical ventilation. However, there is no clear consensus on the timing of ECMO use in severe COVID-19 patients. Objective: The aim of this study is to compare the differences in pre-ECMO time and ECMO duration between COVID-19 survivors and non-survivors and to explore the association between them. Methods: PubMed, the Cochrane Library, Embase, and other sources were searched until 21 October 2022. Studies reporting the relationship between ECMO-related time and COVID-19 survival were included. All available data were pooled using random-effects methods. Linear regression analysis was used to determine the correlation between pre-ECMO time and ECMO duration. The meta-analysis was registered with PROSPERO under registration number CRD42023403236. Results: Out of the initial 2473 citations, we analyzed 318 full-text articles, and 54 studies were included, involving 13,691 patients. There were significant differences between survivors and non-survivors in the time from COVID-19 diagnosis (standardized mean difference (SMD) = −0.41, 95% confidence interval (CI): [−0.53, −0.29], $p < 0.00001$), hospital (SMD = −0.53, 95% CI: [−0.97, −0.09], $p = 0.02$) and intensive care unit (ICU) admission (SMD = −0.28, 95% CI: [−0.49, −0.08], $p = 0.007$), intubation or mechanical ventilation to ECMO (SMD = −0.21, 95% CI: [−0.32, −0.09], $p = 0.0003$) and ECMO duration (SMD = −0.18, 95% CI: [−0.30, −0.06], $p = 0.003$). There was no statistical association between a longer time from symptom onset to ECMO (hazard ratio (HR) = 1.05, 95% CI: [0.99, 1.12], $p = 0.11$) or time from intubation or mechanical ventilation (MV) and the risk of mortality (highest vs. lowest time groups odds ratio (OR) = 1.18, 95% CI: [0.78, 1.78], $p = 0.42$; per one-day increase OR = 1.14, 95% CI: [0.86, 1.52], $p = 0.36$; HR = 0.99, 95% CI: [0.95, 1.02], $p = 0.39$). There was no linear relationship between pre-ECMO time and ECMO duration. Conclusion: There are differences in pre-ECMO time between COVID-19 survivors and non-survivors, and there is insufficient evidence to conclude that longer pre-ECMO time is responsible for reduced survival in COVID-19 patients. ECMO duration differed between survivors and non-survivors, and the timing of pre-ECMO does not have an impact on ECMO duration. Further studies are needed to explore the association between pre-ECMO and ECMO time in the survival of COVID-19 patients.

**Keywords:** COVID-19; pre-ECMO time; ECMO duration; survival

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel form of pneumonia caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. According to the World Health Organization (WHO), globally, as of 21 February 2023, there have been 757,264,511 confirmed cases of COVID-19, including 6,850,594 deaths (URL: https://covid19.who.int/, accessed on 21 February 2023). While most COVID-19 patients experience mild symptoms, several studies suggest that the mortality rate of COVID-19 is still as high as 53–67% [1,2].

In China, the overall case-fatality rate for COVID-19 is 2.3% (1023 deaths out of 44,672 confirmed cases), with approximately 2087 patients in critical condition accounting for 5% of confirmed cases. Among critically ill COVID-19 patients, there were approximately 1023 deaths, resulting in a mortality rate of 49% [3]. Based on the experience of the previous viral outbreak period [4,5], extracorporeal membrane oxygenation (ECMO) has been identified as an important form of life support for critically ill patients. It can be effective in treating severe respiratory failure due to acute respiratory distress syndrome (ARDS) and supporting gas exchange in patients who have failed conventional mechanical ventilation (MV). At the same time, Extracorporeal Life Support Organization (ELSO) guidelines suggest that ECMO can be used as a rescue treatment for critically ill COVID-19 patients who do not respond to conventional ARDS therapy [6].

Despite optimism regarding the potential role of ECMO in COVID-19 treatment, several studies still report a high mortality rate. A meta-analysis found a mortality rate of 37% in patients who received ECMO for COVID-19 in 2020 [7]. Additionally, ELSO registry data reported an increase in mortality rates for the use of ECMO in COVID-19 patients, rising from 37% at the beginning of 2020 to 52% at the end of the year [8,9]. Late initiation of ECMO may be an independent risk factor for increased mortality. Li et al. revealed that early initiation of ECMO was associated with decreased 60-day mortality after ECMO (50% vs. 88%, $p = 0.044$) [10]. However, Mathilde et al. reported that late ECMO treatment in patients with refractory ARDS related to SARS-CoV-2 does not seem to be associated with an excess risk of mortality [11]. The optimal timing for initiating ECMO in COVID-19 treatment is currently uncertain and controversial. There is insufficient global evidence to assess the effectiveness of ECMO timing, and no studies have shown whether ECMO duration affects mortality in severe COVID-19 patients.

To aid clinicians in accurately determining the timing of ECMO use and to improve the use and management of ECMO in severe COVID-19 patients, we conducted a systematic review and meta-analysis. This study focuses on the timing of pre-ECMO and ECMO duration in COVID-19 patients, to clarify the effects of pre-ECMO and ECMO duration on COVID-19 patient survival, and to guide current clinical practice and future research. Furthermore, we have further investigated the linear correlation between pre-ECMO time and ECMO duration.

## 2. Methods

The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews URL: https://www.york.ac.uk/crd/, accessed on 3 March 2023), with the registration number CRD42023403236. This meta-analysis was conducted according to the guidelines of the Preferred Reporting Item for Systematic Review and Meta-Analysis 2020 (PRISMA 2020) (Supplementary Table S1).

### 2.1. Literature Search

Three databases (PubMed, Embase, and the Cochrane Library databases) were used as our search libraries. Other sources, such as the Critical Care Medicine website (URL: http://www.ccmjournal.com, accessed on 21 October 2022), the Critical Care website (URL: http://ccforum.com, accessed on 21 October 2022), and the American Journal of Respiratory and Critical Care Medicine website (URL: http://ajrccm.atsjournals.org, accessed on 21 October 2022), were also searched. Without language restriction, the following search Medical Subject Headings (MeSHs) were used to retrieve advanced articles from inception to 21 October 2022 according to the PICOS (population, intervention/exposure, comparison, outcome, and study design) principle: (1) for patients: "COVID-19" OR "SARS-CoV-2 Infection"; (2) for intervention and comparison: "Extracorporeal Membrane Oxygenations"; (3) for outcome: "Outcome" OR "Survival". Supplementary Table S2 describes the detailed search strategy.

### 2.2. Study Selection

Reference management software, Endnote X9.3.3 software (Thomson Reuters, New York, NY, USA), was used to organize all studies. All titles and abstracts were reviewed after removing duplicates. Then, the full-text assessment was performed following an initial screening to consider eligibility for inclusion.

According to the PICOS principle, the inclusion criteria were as follows: (1) for population: adults (aged > 18 years) who were diagnosed with COVID-19 infection by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay and who underwent ECMO for hypoxemia; (2) for intervention, comparison, and outcome: studies on the association between differences in the duration of ECMO and patient survival, reporting corresponding risk estimates, such as odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs), and their corresponding 95% confidence intervals (CIs), or providing related data; (3) for study design: random controlled trials (RCTs), post hoc analyses of RCTs, observational cohort studies, and cross-sectional studies.

Our exclusion criteria included: (1) reviews and studies with insufficient data; (2) populations with other established conditions (e.g., diabetes population) at baseline; and (3) if the same population was used in multiple studies, we excluded the less informative article.

### 2.3. Data Extraction and Quality Assessment

Data extraction and quality assessment of the included studies were conducted independently by two researchers. Information extracted included author, year of publication, country, study design, data source, follow-up time, sample size, mean age, gender, ECMO type, ECMO initiation, baseline comorbidities, other treatment, time period category, baseline data, estimated effect, and adjustments.

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included observational studies. The scores range from zero to nine to evaluate the selection, comparability, and outcome of articles. Studies with NOS scores of one to three, four to six, and seven to nine are considered to be of low, medium, and high quality, respectively [12,13].

### 2.4. Statistical Analysis

All data (e.g., age, time) expressed as quartiles and medians were converted to the mean and standard deviation [14–16]. To elucidate the differences in baseline pre-ECMO and ECMO time between survivors and non-survivors in severe COVID-19 patients, we respectively pooled the pre-ECMO (time from symptom onset to ECMO, time from COVID-19 diagnosis to ECMO, time from hospital admission to ECMO, time from intensive care unit (ICU) admission to ECMO, and time from MV or intubation to ECMO) and ECMO time of survivors and non-survivors using the inverse-variance method and random model to generate the effect size standardized mean difference (SMD).

OR is approximately equivalent to RR or HR when the outcome is rare [17]. Therefore, to determine the relationship between time and survival, the ORs, RRs, and HRs and their 95% CIs were pooled, respectively, using a random-effects model to improve reliability. We estimated the effect size by calculating the natural logarithm of the OR, RR, or HR (log [OR], log [RR], or log [HR]) and their standard error (SElog [OR], SElog [RR], or SElog [HR]) to be pooled. Pre-ECMO and ECMO time were analyzed as a categorical variable, with the group with the longest time compared to the group with the shortest time. Time was analyzed as a continuous variable, and the units of the time (per one-day increase) were standardized.

A linear regression model was used to identify directional associations between ECMO duration and pre-ECMO time, including time from symptom onset to ECMO, time from COVID-19 diagnosis to ECMO, time from hospital admission to ECMO, time from ICU admission to ECMO, and time from MV or intubation to ECMO.

SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA) and Review Manager (RevMan) version 5.4 (The Cochrane Collaboration 2014; Nordic Cochrane Center Copen-

hagen, Denmark) were used for statistics and analysis. A *p*-value of < 0.05 was considered statistically significant.

### 2.5. Heterogeneity Test, Publication Bias, and Sensitivity Analysis

We calculated the statistical *p*-value using the Q-test, with a *p*-value < 0.1 representing a significant difference between the two groups. To estimate the degree of heterogeneity, we applied the $I^2$ test between studies. Low heterogeneity, moderate heterogeneity, and high heterogeneity were defined as $I^2$ < 50%, 50–75%, and >75%, respectively [18]. Sensitivity analyses were performed by omitting each study in turn.

## 3. Results

### 3.1. Literature Search

Figure 1 shows the flowchart of the database search process. According to the preformulated search protocol, a total of 2473 publications were identified in the initial search (PubMed = 1697; Cochrane Library = 21; Embase = 532; other sources = 223). After excluding 528 duplicates and 1627 irrelevant publications after title and abstract screening, 318 articles were processed for full-text assessment. After removing 114 articles with specific publication types without data, a further 150 articles were excluded for the following reasons: (1) studies without data of interest (*n* = 23); (2) duplicated cohorts (*n* = 5); (3) studies without full text (*n* = 24); (4) studies not focusing on pre-ECMO or ECMO time (*n* = 37); (5) studies not focusing on specific populations (*n* = 10); (6) studies not focusing on target outcome (*n* = 19); and (7) case reports (*n* = 32). All excluded studies (*n* = 150) and their corresponding reasons are listed in Supplementary Table S3. Ultimately, our meta-analysis included a total of 54 studies with 55 cohorts [19–72].
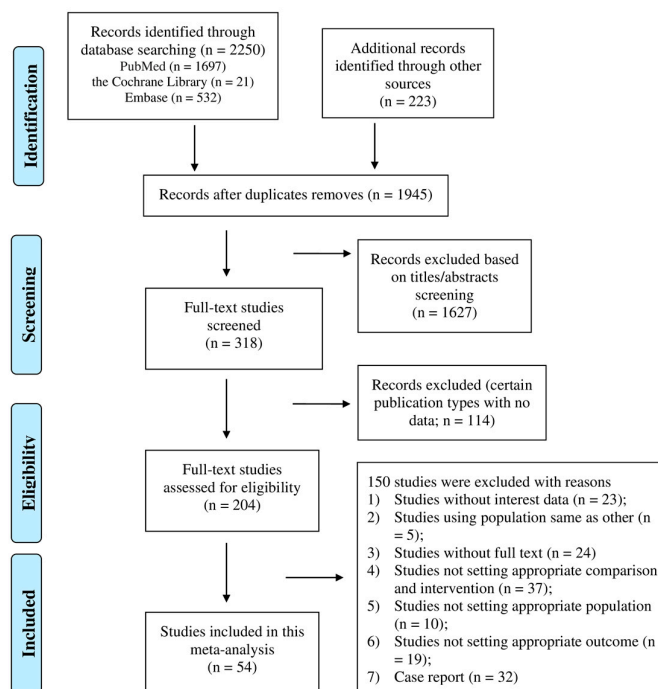


**Figure 1.** Flow chart of study selection in the systematic review and meta-analysis of ECMO time difference in the survival of COVID-19.

Other sources include the Critical Care Medicine website, the Critical Care website, and the American Journal of Respiratory and Critical Care Medicine website.

### 3.2. Study Characteristics

The basic characteristics of all included studies are shown in Table 1. Fifty-four cohort studies [19–72] were published from 2020 to 2022, including 13,691 severe COVID-

19 patients on ECMO, with a mean age ranging from 44 to 67 years. The sample size ranged from 11 to 7135, and the duration of follow-up from ECMO decannulation to two years. Of these articles, seventeen cohorts reported the time from symptom onset to ECMO [22,24,26,31,39,40,42,44,50,54–56,61,63,65,67,70], four reported the time from COVID-19 diagnosis to ECMO [34,38,47,52], eleven reported the time from hospital admission to ECMO [20,24,25,39,42,46,48,61,64,66,71], four reported time from ICU admission to ECMO [23,29,44,61], thirty-nine reported time from intubation or MV to ECMO [19,24,26–30,33–40,42–45,47,50–59,61,62,64,66–68,70–72], thirty-five reported duration of ECMO [19–21,23,24,27–29,32–39,41–50,55,58,61,63,66,69–72]. Of the total articles, twenty-four studies were conducted in the Americas (twenty-two in the United States of America (USA) [19–21,24,25,32,34,35,38,39,46,47,52,54,55,57,58,61,65,66,68,70], one in Argentina [26], one in Chile [29]), twenty-three in Europe (nine in France [22,29,33,42,44,49,50,59,60], six in Germany [31,37,41,48,62,71], two in the United Kingdom of Great Britain and Northern Ireland (UK) [27,72], two in Spain [51,56], one in Finland [23], one in Austria [36], one in Poland [64], one in Italy [45]), seven in Asia (three in China [28,40,67], two in Japan [63,69], one in Republic of Korea [43], one in Saudi Arabia [53]). In addition, forty-two of them were retrospective cohort studies [19–21,23,24,26,27,30–32,35–37,39–48,50,52–54,57–65,67–72], ten were prospective cohort studies [22,25,28,33,34,38,49,51,55,66], and two were ambispective cohort studies [29,56].

Table 1. Basic characteristics of the articles included in the meta-analysis.

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Akkanti, 2022, USA [19] | Retrospective cohort | Baylor St. Luke's Medical Center, Houston Methodist Hospital, or University of Texas Memorial Herrmann Hospital between 15 March 2020, and 30 May 2020 | 2 years, 35 | 49, 43 | VV ECMO and VA ECMO. | ELSO guidelines | 66% obesity; 48% hypertension; 29% diabetes; 8% dialysis for AKI; 6% asthma | 83% convalescent plasma; 31% remdesivir; 68% anti-IL-6 therapies | from intubation to ECMO / ECMO duration | 4.66 ± 3.52; 3.20 ± 2.38 / 13.95 ± 11.74; 16.6 ± 15.77 | |
| Alnababteh, 2021, USA [20] | Respective cohort | MedStar Washington Hospital Center from 23 March 2020 to 29 April 2020 | Until ICU discharge, 13 | 45, 62 | VV ECMO | EOLIA trial | 38.5% hypertension; 30.8% diabetes | 100% prone; 76.9% azithromycin; 76.9% hydro chloroquine; 69.2% IL-6 inhibitor; 100% neuromuscular blockade; 76.9% inhaled epoprostenol; 92.3% anticoagulation | From admission to ECMO / ECMO duration | 7.49 ± 4.02; 2.92 ± 4.34 / 12.26 ± 4.29; 15.85 ± 11.61 | |
| Bergman, 2021, USA [21] | Retrospective cohort | one of four adult ELSO-certified Centers of Excellence in Minnesota (University of Minnesota MHealth Fairview, Hennepin County Medical Center, Abbott Northwestern Hospital, and Mayo Clinic Rochester) from 1 March 2020 through 1 November 2020 | 60 days, 46 | 51, 83 | VV ECMO and VAV ECMO | (1) On FiO$_2$ ≥ 80%, PEEP ≥ 10, and VT ≤ 6 mL/kg PBW; (2) PaO$_2$/FiO$_2$ < 50 for more than 3 h; (3) PaO$_2$/FiO$_2$ < 80 for more than 6 h; (4) pH < 7.25, PaCO$_2$ > 60 mmHg with RR > 35 for more than 6 h | 41.3% obesity; 45.7% hypertension; 28.3% hyperlipidemia; 39.1% diabetes; 8.7% asthma/COPD; 6.5% CAD; 13% CKD | 19.6% hydroxychloroquine + azithromycin; 67.4% remdesivir; 56.5% IL-6 inhibitor; 47.8% convalescent plasma; 45.7% steroids | ECMO duration | 21.50 ± 14.79; 31.55 ± 17.88 | |
| Beyls, 2021, France [22] | Prospective cohort | Amiens University Hospital between 28 February 2020 and 1 June 2020, 1 September 2020 and 15 April 2020 and between 12 December 2020 and 15 June 2021 | 90 days, 54 | 58, 74 | VV ECMO | ELSO guidelines | 1% hypertension; 4% diabetes; 17% dyslipidemia; 7% chronic renal disease; 9% COPD/asthma; 7% coronary disease; 6% immunocompromised | 81% glucocorticoids; 17% lopinavir-ritonavir; 7% hydroxychloroquine; 4% tocilizumab | From symptom onset to ECMO | | HR 1.10 (1.02–1.17); multivariate adjustment |
| Biancari, 2021, Finland [23] | Retrospective cohort | ten ECMO centers in five European countries (France, Germany, Italy, Sweden, UK) between 2 March 2020 and 30 April 2020 | 6 months, 132 | 51, 83 | VV ECMO, VA ECMO, VA ECMO and VVA ECMO | NA | 11.4% dialysis; 22% diabetes; 3% cancer; 28.8% hypertension; 9.2% asthma/COPD; 0.8% congestive heart failure; 3% CAD; 1.5% stroke/transient ischemic attack | 93.2% prone positioning; 4.5% convalescent plasma; 25% hydroxychloroquine/choloroquine; 6.8% extracorporeal cytokine absorber; 6.8% tocilizumab; 35.6% corticosteroids | from ICU admission to ECMO / ECMO duration | 5.30 ± 5.50; 6.20 ± 5.20 / 15.10 ± 9.80; 14.10 ± 12.00 | |
| Blazoski, 2021, USA [24] | Retrospective cohort | Thomas Jefferson University from 1 April 2020 to 11 June 2020 | NA, 20 | 54, 60 | VV ECMO and VA ECMO | NA | 10% chronic lung disease; 30% diabetes; 5% liver failure; 5% chronic immunosuppression; 30% acute renal injury | 40% steroids; 55% IL inhibitor; 20% remdesivir; 15% plasma | From symptom onset to ECMO / From hospital admission to ECMO / from MV to ECMO / ECMO duration | 9.90 ± 4.60; 13.50 ± 8.40 / 12.00 ± 16.00; 8.80 ± 7.70 / 8.58 ± 14.33; 3.17 ± 2.83 / 11.00 ± 6.20; 17.00 ± 12.00 | |
| Braaten, 2022, USA [25] | Prospective cohort | one of the four adult ECMO centers in the state of Minnesota (University of Minnesota, Hennepin County Medical Center, Abbott Northwestern Hospital, and the Mayo Clinic Rochester) from March 2020 to May 2021 | 60 days, 100 | 52, 75 | VV ECMO | NA | 32% hypertension; 28% hyperlipidemia; 32% diabetes; 11% asthma/COPD; 7% chronic artery disease; 11% CKD | 23% hydroxychloroquine + azithromycin; 59% remdesivir; 39% IL-6 inhibitor; 46% convalescent plasma; 86% steroids | From hospital admission to ECMO | 6.65 ± 3.81; 10.00 ± 6.11 | |
| Casabella, 2021, Argentina [26] | Retrospective cohort | During the first surge in Argentina | NA, 26 | 50, 80 | NA | NA | NA | NA | From symptom onset to ECMO / From MV to ECMO | 12.12 ± 5.25; 18.99 ± 11.72 / 5.19 ± 4.81; 6.72 ± 5.66 | |
| Charlon, 2021, UK [27] | Retrospective cohort | one of the commissioned UK respiratory ECMO centers from 1 April to 31 May 2020 | NA, 34 | 44, 79 | NA | NA | 23.5% hypertension; 11.8% diabetes; 67.6% obese | NA | From MV to ECMO | 5.20 ± 1.80; 4.60 ± 1.70 | |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cheng, 2021, China [28] | Prospective cohort | 62 authorized hospitals in Wuhan from 1 January 2020, to 1 May 2020 | 90 days, 74 | 57, 62 | NA | (1) $PaO_2/FiO_2 < 50$ mmHg for more than 3 h; (2) $PaO_2/FiO_2 < 80$ mmHg for more than 6 h; (3) $FiO_2 = 1.0$, $PaO_2/FiO_2 < 100$ mmHg; (4) pH $< 7.25$ and $PaCO_2 > 60$ mmHg for more than 6 h, with RR > 35/min; (5) pH $< 7.2$ and plateau pressure > 30 $cmH_2O$, even respiratory rate > 35/min; (6) severe air leakage syndrome | 40.5% hypertension; 29.7% diabetes; 28.4% cardiovascular disease; 2.7% chronic pulmonary disease; 10.8% CKD; 10.8% chronic liver disease; 1.4% digestive disease; 9.5% cerebral vascular disease | 39.2% prone position; 97.3% vasoactive drugs; 45.9% anti-viral drugs; 91.9% cortical steroids; 9.5% tocilizumab | ECMO duration; From intubation to ECMO; ECMO duration | 11.10 ± 4.90; 15.60 ± 5.60; 3.80 ± 5.57; 5.53 ± 5.72; 10.54 ± 7.39; 15.35 ± 9.91 | |
| Daviet, 2021, France [29] | Ambispective cohort | tertiary University Hospital of Assistance Publique-Hôpitaux de Marseille France, constituted of 5 different ICU units from 1 March 2020 to 31 May 2020 and 1 September 2020 to 30 November 2020 | 90 days, 76 | 60, 78 | VV ECMO and VA ECMO | NA | 38% obesity; 42.1% hypertension; 36.8% diabetes; 11.8% CAD; 21.1% dyslipidemia; 6.6% immunosuppression; 11.8% chronic lung disease; 5.3% chronic kidney disease | 67% dexamethasone; 32% hydroxychloroquine; 4% antiviral treatment; 8% anti-IL 6; 16% anti-IL 1; 18% junus kinase 1/2 inhibitor; 62% high-dose corticosteroid | From ICU admission to ECMO; From MV to ECMO; ECMO duration | 7.94 ± 5.39; 11.00 ± 4.63; 5.71 ± 4.62; 7.00 ± 6.17; 15.42 ± 10.78; 27.00 ± 18.51 | OR 1.18 (0.98–1.40); adjusted for age, BMI, PRESERVE score, Charlson score |
| Diaz, 2021, Chile [30] | Retrospective cohort | Any of the 13 ECMO centers in Chile from 3 March through 31 August 2020 | Until 3 March 2021, 85 | 48, 84 | VV ECMO (three patients unclear) | Based on the ELSO COVID-19 guidelines | 30.6% hypertension; 21.2% diabetes; 42.4% obesity; 7.1% COPD/asthma | 91.8% prone positioning; 94.1% neuromuscular blockade | From intubation to ECMO | 4.85 ± 4.57; 4.00 ± 3.10 | HR 0.96 (0.90–1.02); univariate adjustment |
| Dreier, 2021, Germany [31] | Retrospective cohort | ICUs of the University Hospital Regensburg between 25 March and 7 May 2020 | 6 months, 16 | 58, 81 | VV ECMO | NA | 12.5% chronic pulmonary disease; 37.5% arterial hypertension; 6.3% CKD; 18.8% diabetes | NA | From symptom onset to ECMO | 16.20 ± 5.94; 27.39 ± 5.03 | |
| Gannon, 2022, USA (Derivation cohort) [32] | Retrospective cohort | International ELSO Registry data from at the time of initial data pull in April 2021 | NA, 4553 | 50, 73 | VV ECMO | NA | 30% diabetes; 35.8% hypertension; 3.6% cardiac disease; 4% respiratory disease; 2.9% renal insufficiency; 9.6% central nervous system dysfunction; 4% immunocompromised; 1.8% cancer; 12.8% pneumothorax; 3.3% cardiac arrest; 28.1% acute renal failure | 74.5% neuromuscular blocking agent; 60.4% prone positioning; 31.1% inhaled pulmonary vasodilators | ECMO duration | 17.94 ± 14.91; 19.96 ± 15.50 | |
| Gannon, 2022, USA (Validation cohort) [32] | | International ELSO Registry data between April 2021 and October 2021 | NA, 2582 | 47, 68 | VV ECMO | | 24.2% diabetes; 34.8% hypertension; 2.5% cardiac disease; 3.8% respiratory disease; 2.4% renal insufficiency; 10.2% central nervous system dysfunction; 2.9% immunocompromised; 1.0% cancer; 15.7% pneumothorax; 3.1% cardiac arrest; 23.7% acute renal failure | 70.6% neuromuscular blocking agent; 56.3% prone positioning; 31.4% inhaled pulmonary vasodilators | ECMO duration | 21.99 ± 20.11; 22.97 ± 18.33 | |
| Hajage, 2022, France [33] | Prospective cohort | University Hospitals of Geneva between 25 February 2020, and 4 May 2020 | 90 days, 269 | 53, 77 | NA | Patients in ICU and on IMV, with time spent in ICU < 14 days (before ECMO initiation) and time spent on IMV < 7 days, age < 70 years, SAPS II at ICU admission 90 or less, and $PaO_2/FiO_2$, 80 mmHg or $PaCO_2 < 60$ mmHg | 31% hypertension; 24% diabetes | 89% prone position; 97% neuromuscular blockade; 50% NO; 22% corticosteroids | From MV to ECMO; ECMO duration; From COVID-19 diagnosis to ECMO | 5.00 ± 2.99; 6.70 ± 3.00; 13.05 ± 9.73; 9.35 ± 6.75; 10.44 ± 8.03; 14.30 ± 7.45 | |
| Hall, 2022, USA [34] | Prospective cohort | multi-institutional SCOPE Registry database supported with ECMO at 45 hospitals located in 21 US states between 17 March 2020 and 11 October 2021 | 19 months, 505 | 48, 69 | VV ECMO and VA ECMO | NA | 13% asthma; 2.16% cancer; 7.68% chronic renal failure; 37.7% diabetes; 9.54% heart disease; 46.1% hypertension; 64% obesity | 73.1% antiviral medication; 49.5% convalescent plasma; 12.6% hydroxychloroquine; 35.3% IL-6 blocker; 34.9% prostaglandin; 85.2% steroids | From intubation to ECMO; ECMO duration | 3.41 ± 3.55; 4.00 ± 4.47; 16.68 ± 12.55; 20.18 ± 13.78 | OR 0.82(0.49–1.38); multivariate adjustment |
| Haroun, 2022, USA [35] | Retrospective cohort | Montefiore Medical Center and other invited centers between 1 March 2020, and 30 April 2021 | Until the time of discharge and/or transfer or in-hospital mortality, 37 | 44, 68 | VV ECMO, VA ECMO, and VAV ECMO | NA | 32% hypertension; 30% diabetes; 5% CAD | 62% prone positioning; 72% vasopressors; 38% inotropes | From intubation to ECMO | 1.46 ± 3.32; 3.07 ± 3.94 | |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hermann, 2022, Austria [36] | Retrospective cohort | Medical University of Vienna, from January 2020 until May 2021 | NA, 101 | 56, 70 | VV ECMO, VA ECMO, and VVA ECMO | the official Medical University of Vienna consensus recommendations | 59% arterial hypertension; 13% CAD; 35% obesity; 25% diabetes; 19% underlying pulmonary disease; 3% immunosuppression; 6% CKD | 100% prone positioning; 21% inhaled NO; 6% tracheostomy | ECMO duration | 22.49 ± 24.92; 24.18 ± 24.82 | HR 0.93 (0.88–0.98); adjusted for the baseline condition of patients |
| | | | | | | | | | From MV to ECMO | 7.59 ± 7.60; 7.79 ± 6.45 | |
| Herrmann, 2022, Germany [37] | Retrospective cohort | 26 ECMO centers across Germany between 1 January 2020 and 22 March 2021 | NA, 673 | NA, 79 | VV ECMO, VA ECMO, and VVA ECMO | at the discretion of the respective centers according to their in-house standards | 61.8% cardiovascular disease; 27.6% diabetes; 15.3% chronic pulmonary disease; 7.3% kidney disease | 49.5% prone positioning; 92.1% therapeutic anticoagulation | ECMO duration | 18.55 ± 13.06; 15.21 ± 13.67 | OR 1.30 (0.76–2.22); adjusted for demographics, risk factors and comorbidities (age, sex, BMI, and immunosuppression within 6 months prior to admission), severity of disease (intubation prior to ECMO and EOLIA criteria), ECMO case volume, and complications (major bleeding or thromboembolic events, secondary bacterial infection, and renal replacement therapy) |
| | | | | | | | | | From MV to ECMO | NA | |
| Jacobs, 2022, USA [38] | Prospective cohort | 29 hospitals in 18 states in the US from 17 March 2020 to 1 December 2020 | NA, 200 | 50, 69 | VV ECMO and VA ECMO | determined by the individual patient care teams at each of the contributing 29 hospitals | 16.5% asthma; 3% cancer; 6% chronic renal failure; 38% diabetes; 11% heart disease; 47% hypertension; 64% obesity | 63.3% prone position before ECMO; 35% tracheostomy; 54.5% antiviral medication; 52.4% convalescent plasma; 23% hydroxychloroquine; 38.4% IL-6 blocker; 41.7% prostaglandin; 72% steroids | ECMO duration | 14.98 ± 11.90; 12.83 ± 11.85 | |
| | | | | | | | | | From COVID-19 diagnosis to ECMO | 9.10 ± 6.76; 12.80 ± 8.96 | |
| | | | | | | | | | From intubation to ECMO | 4.18 ± 3.80; 5.30 ± 5.30 | |
| | | | | | | | | | ECMO duration | 19.30 ± 16.40; 21.00 ± 15.90 | |
| Kunavarapu, 2021, USA [39] | Retrospective cohort | a tertiary referral high-volume ECMO center between 3 October 2020 and 8 April 2020 | NA, 52 | 48, 67 | VV ECMO and VA ECMO | EOLIA trial | 46.2% hypertension; 30.8% diabetes; 13.5% asthma | 19.2% prior use of ACEi/ARB; 38.5% tracheostomy; 51.9% vasopressors; 76.9% convalescent plasma; 11.5% continuous renal replacement therapy | From symptom onset to ECMO | 11.40 ± 4.80; 14.40 ± 5.50 | OR 1.31 (1.0–1.7); multivariate adjustment |
| | | | | | | | | | From hospital admission to ECMO | 4.70 ± 3.80; 6.40 ± 4.60 | |
| | | | | | | | | | From intubation to ECMO | 2.10 ± 2.60; 2.80 ± 2.60 | |
| | | | | | | | | | ECMO duration | 20.40 ± 24.50; 21.50 ± 17.90 | |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lai, 2021, China [40] | Retrospective cohort | all adult COVID-19 patients (age from 35 to 91) from Beijing, Sichuan, Guangxi, Hunan, and Hebei province in China who received ECMO support between 3 February 2020, and 23 January 2021 | Until died within 48 h or discharge, 50 | 66, 68 | VV ECMO and VA ECMO | (1) developed a refractory severe ARDS; (2) Lung Injury Murray Score $\geq$ 3; (3) developed uncompensated hypercapnia with pH < 7.25 or $PaCO_2$ > 60 mmHg over 6 h; (4) $PaO_2/FiO_2$ < 80 over 6 h; (5) $PaO_2/FiO_2$ < 50 mm Hg over 3 h evaluated by an interdisciplinary team of at least one ECMO specialist, a registered nurse, and a perfusionist following local standards | 30% diabetes; 44% hypertension | NA | From symptom onset to ECMO | 14.60 ± 10.73; 17.80 ± 15.98 | |
| | | | | | | | | | From MV to ECMO | 3.23 ± 3.18; 6.24 ± 7.41 | |
| Lang, 2021, Germany [41] | Retrospective cohort | university hospital of Freiburg from 3 August 2020 to 4 August 2020 | Until 28 May 2020, 34 | 67, 82 | VV ECMO | | 52.9% hypertension; 35.3% diabetes; 23.5% CAD; 17.6% other cardiac disease; 23.5% CKD; 23.5% cancer; 11.8% immunosuppression | 88.2% positioning maneuvers; 35.3% renal replacement therapy; 82.4% vasopressor therapy | ECMO duration | 16.00 ± 7.00; 22.00 ± 30.00 | |
| Lebreton, 2021, France [42] | Retrospective cohort | any Greater Paris ICU between 8 March and 3 June 2020 | 90 days, 302 | 52, 78 | VV ECMO, VA ECMO and VAV ECMO | EOLIA trial | 34% hypertension; 29% diabetes; 3% ischemic cardiomyopathy; 11% chronic respiratory disease; 6% immunocompromised | 96% neuromuscular blockade; 94% prone positioning; 56% inhaled NO or prostacyclin; 20% steroids; 12% renal replacement therapy; 20% tracheostomy | From symptom onset to ECMO | 13.35 ± 5.24; 14.70 ± 5.98 | |
| | | | | | | | | | From hospital admission to ECMO | 6.35 ± 3.75; 7.70 ± 4.49 | |
| | | | | | | | | | From intubation to ECMO | 4.00 ± 3.00; 5.35 ± 3.74 | OR 0.91 (0.84–0.99); multivariate adjustment |
| | | | | | | | | | ECMO duration | 18.05 ± 12.74; 14.46 ± 14.21 | |
| Lee, 2022, Republic of Korea [43] | Retrospective cohort | 1200-bed tertiary academic hospital and ECMO referral center in Republic of Korea from January 2020 to December 2021 | NA, 39 | 64, 59 | VV ECMO, VA ECMO and VAV ECMO | Decided by consulting with the internal medicine department | 51.3% hypertension; 41% diabetes; 2.6% COPD; 10.3% heart failure; 2.6% liver cirrhosis; 2.6% CKD; 10.3% malignancy | 61.5% remdesivir; 79.5% antibiotics; 74.4% vasopressor; 97.4% steroid. 17.9% tocilizumab; 25.6% continuous renal replacement therapy | From MV to ECMO | 1.10 ± 2.49; 12.61 ± 6.67 | |
| | | | | | | | | | ECMO duration | 12.64 ± 7.06; 19.43 ± 21.02 | |
| Levy, 2022, France [44] | Retrospective cohort | A 50-bed mixed ICU from October 2020 to June 2021 | 7 days, 11 | 52, 82 | VV ECMO | NA | 27.3% diabetes; 18.2% COPD; 18.2% coronary disease | NA | From symptom onset to ECMO | 21.78 ± 23.13; 18.57 ± 10.01 | |
| | | | | | | | | | From ICU admission to ECMO | 16.11 ± 22.12; 11.38 ± 10.49 | |
| | | | | | | | | | From MV to ECMO | 8.42 ± 19.61; 8.35 ± 9.53 | |
| | | | | | | | | | ECMO duration | 21.89 ± 22.12; 26.24 ± 13.35 | |
| Loforte, 2021, Italy [45] | Retrospective cohort | 12 ECMO hub venters across Italy between 1 March and 15 September 2020 | Until 30 September 2020, 71 | 55, 86 | VV ECMO and VAV ECMO | a multidisciplinary team assessment | 16.9% diabetes; 43.7% hypertension; 8.5% CAD; 7% atrial fibrillation; 2.8% concomitant heart disease; 7% asthma/COPD; 4.2% CKD; 2.8% dialysis | 15.5% ACEi; 8.5% ARBs; 100% IMV; 70.4% antiretroviral therapy; 85% prone positioning; 85% neuromuscular blockade; 19.7% epinephrine; 77.5% norepinephrine; 18.3% inhaled pulmonary vasodilators | From MV to ECMO | 4.99 ± 4.00; 4.23 ± 3.68 | |
| | | | | | | | | | ECMO duration | 14.36 ± 14.90; 15.71 ± 9.19 | |
| Maharaj, 2022, USA [46] | Retrospective cohort | University of Minnesota between January 2020 and December 2020 | NA, 17 | 48, 65 | VV ECMO | NA | 65% diabete; 53% hypertension; 12% COPD | 35% home ACEi/ARB/ARNI use; 76% prone positioning | From hospital admission to ECMO | 5.44 ± 5.42; 9.78 ± 5.76 | |
| | | | | | | | | | ECMO duration | 18.76 ± 12.86; 30.85 ± 18.06 | |
| Mongero, 2021, USA [47] | Retrospective cohort | 40 institutions from SCOPE between 18 March 2021 | Until discharge, 342 | 49, 71 | VV ECMO and VA ECMO | NA | 14.9% asthma; 2.68% cancer; 8.46% chronic renal failure; 37.6% diabetes; 10.7% heart disease; 47.9% hypertension | 67.5% prone before ECMO | From COVID-19 diagnosis to ECMO | 11.25 ± 9.03; 13.70 ± 9.72 | |
| | | | | | | | | | From intubation to ECMO | 4.15 ± 3.88; 4.86 ± 4.73 | |
| | | | | | | | | | ECMO duration | 19.80 ± 15.50; 23.40 ± 19.10 | |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Natanov, 2022, Germany [48] | Retrospective cohort | Hannover medical school center between January 2020 and August 2021 | NA, 85 | 55, 84 | VV ECMO | ELSO guidelines | 16.5% COPD; 23.5% II diabetes mellitus; 15.3% cardiovascular disease; 10.6% renal insufficiency; 47.1% arterial hypertension; 81.2% obesity | 96.5% administration of antibiotics; 23.5% administration of antivirals; 1.2% inotropes; 74.1% vasopressors; 87.1% prone position | From hospital admission to ECMO / ECMO duration | 8.10 ± 1.30; 12.10 ± 1.20 / 12.40 ± 1.50; 18.20 ± 1.90 | |
| Nesserler, 2022, France [49] | Prospective cohort | ECMOSARS registry from before 21 April 2020 up to 25 October 2020 | 90 days, 429 | 53, 79 | VA ECMO and VV ECMO | NA | 38% hypertension; 30% diabetes; 3% COPD; 3% chronic respiratory failure; 1% congestive heart failure; 5% CAD; 4% CKD; 2% cancer | 6% steroids; 2% NSAIDs; 10% ACEi; 14% ARBs | From MV to ECMO | | HR 1.74 (1.07–2.83); adjusted for patient-related confounders (sex, age, BMI, diabetes, COPD, chronic respiratory failure, congestive heart failure, CKD, malignancy, and previous corticotherapy) and pre-ECMO hospitalization-related confounders (septic shock, total bilirubin at cannulation, pH at cannulation, $PaCO_2$ fractional inspired oxygen tension ($FiO_2$) at cannulation, $PaO_2$) ratio at cannulation, driving pressure, left ventricular ejection fraction, ventilator-associated pneumonia, and delay from hospitalization to ICU admission) |
| Olivier, 2021, France [50] | Retrospective cohort | three French ECMO centers from March 2020 to June 2021 | NA, 56 | 58, 88 | VV ECMO | EOLIA trial criteria | 52% hypertension; 29% diabetes | 100% prone position; 100% neuromuscular blockers | ECMO duration / From symptom onset to ECMO / From intubation to ECMO / ECMO duration | 14.05 ± 9.70; 12.75 ± 11.19 / 15.86 ± 7.83; 18.71 ± 9.36 / 6.71 ± 9.39; 6.71 ± 4.68 / 19.07 ± 18.00; 20.57 ± 15.59 | |
| Pacheco, 2020, Spain [51] | Prospective cohort | Vall d'Hebron University Hospital from 15 March to 30 July 2020 | NA, 24 | 52, 58 | Mainly VV ECMO | $PaO_2$/$FiO_2$ < 80 mmHg, refractory to prone position, and/or $PaCO_2$ > 80 mmHg and pH < 7.25 for >6 h | NA | NA | From MV to ECMO | | OR 1.31 (1.11–1.67); univariate adjustment |
| Powell, 2022, USA [52] | Retrospective cohort | Shock Trauma Center and the University of Maryland Medical Center from 1 January 2020, to 28 July 2021 | Until discharge, 93 | 44, 71 | VV ECMO | NA | 10.8% asthma/COPD; 23.7% diabetes; 1.1% congestive heart failure; 1.1% liver disease | 70.9% vasopressor; 18.3% inotrope; 67.7% prone position; 95.7% paralysis; 16.1% inhaled pulmonary vasodilator; 78.5% steroids; 39.8% convalescent plasma; 60.2% remdesivir; 23.7% monoclonal antibody | From COVID-19 diagnosis to ECMO / From intubation to ECMO | 8.56 ± 7.59; 11.00 ± 4.67 / 2.71 ± 3.03; 2.36 ± 2.34 | |
| Rabie, 2021, Saudi Arabia [53] | Retrospective cohort | 19 ECMO centers in five countries of the SWAAC-ELSO region between 1 March 2020, and 30 September 2020 | Discharge or decannulation, 307 | 45, 81 | VA ECMO, VV ECMO, and VAV ECMO | ELSO guidelines | 31.9% diabetes; 15.3% hypertension; 5.9% COPD/asthma; 2.6% ischemic heart disease | 58.3% vasopressor; 52.1% prone | Pre-ECMO MV | | OR 1.68 (0.90–3.19); multivariate adjustment |
| Raff, 2020, USA [54] | Retrospective cohort | University of North Carolina Medical Center from 1 April to 31 July 2020 | NA, 25 | 47, 72 | VV ECMO | NA | 48% diabetes | NA | From symptom onset to ECMO / From ICU admission to ECMO / From MV to ECMO | 12.40 ± 8.40; 19.90 ± 7.30 / / 3.50 ± 5.50; 6.10 ± 4.20 | RR 1.04 (1.01–1.09); multivariate adjustment |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rajajee, 2020, USA [55] | Prospective cohort | University of Michigan Medical School from 1 March 2020, to 31 July 2020 | 1 year, 23 | 45, 65 | VV ECMO and VA ECMO | persistent severe hypoxemia despite maximal MV and rescue approaches and no absolute contraindications presents | NA | 70% continuous renal replacement therapy; 39% hemodialysis; 35% glucocorticoids; 22% tocilizumab; 9% remdesivir | From symptom onset to ECMO; From intubation to ECMO; ECMO duration | 14.73 ± 9.88; 18.00 ± 10.50 8.09 ± 4.11; 6.00 ± 7.00 16.00 ± 6.59; 19.88 ± 38.05 | |
| Riera, 2022, Spain [56] | Retrospective-prospective cohort study | 24 ECMO centers (22 in Spain and two in Portugal) from 1 March to 1 December 2020 | 6 months, 319 | 53, 81 | NA | EOLIA trial | 37.9% hypertension | NA | From symptom onset to ECMO; From MV to ECMO | | HR 1.009 (0.991–1.027); univariate adjustment HR 1.028 (1.003–1.053); multivariate adjustment HR 1.01 (0.98–1.03); adjusted for age, sex, BMI, cardiopulmonary resuscitation prior to ECMO, transferred to ECMO hospital, prone position prior to ECMO, time from symptoms to intubation, and $PaCO_2$ before ECMO placement, use of intravenous steroids |
| Saeed, 2022, USA [57] | Retrospective cohort | Montefiore Medical Center invited 17 centers between 1 March 2020 and 30 April 2021 | 90 days, 435 | 48, 71 | VV ECMO | NA | 65% hypertension; 50% diabetes; 4% chronic respiratory disease; 2% malignant neoplasm; 6% CAD; | 77% prone positioning; 61% vasopressors | From intubation to ECMO | | |
| Saeed, 2022, USA [58] | Retrospective cohort | Montefiore Medical Center invited 17 centers between 1 March 2020 and 30 September 2020 | 90 days, 292 | 49, 72 | VV ECMO, VA ECMO and VAV ECMO | NA | 41% hypertension; 31% diabetes; 3% chronic respiratory disease; 1% malignant neoplasm; 4% CAD; | 77% prone positioning; 64% vasopressors | From intubation to ECMO; ECMO duration | 3.00 ± 3.00; 3.65 ± 3.75 16.41 ± 11.99; 21.81 ± 21.04 | |
| Schmidt, 2020, France [59] | Retrospective cohort | Paris–Sorbonne University Hospital Network ICUs (three at La Pitié–Salpêtrière Hospital, one in Saint-Antoine Hospital, and one in Tenon Hospital) from 8 March to 2 May 2020 | 60 days, 83 | 49, 73 | VV ECMO, VA ECMO and VAV ECMO | (1) partial pressure of arterial oxygen over a $FiO_2$ ratio of less than 50 mmHg for more than 3 h; (2) $PaO_2/FiO_2$ less than 80 mmHg for more than 6 h; or (3) arterial blood pH less than 7.25 with a partial pressure of arterial $CO_2$ of 60 mmHg or more for 6 h or more | 39% hypertension; 31% diabetes; 5% ischemic cardiomyopathy; 11% chronic respiratory disease/COPD/asthma; 4% immunocompromised | 96% neuromuscular blockade; 94% prone positioning; 34% inhaled NO or prostacyclin; 7% steroids; 1% almitrine; 5% renal replacement therapy | From intubation to ECMO | 3.65 ± 2.29; 6.00 ± 3.11 | |
| Schmidt, 2021, France [60] | Retrospective cohort | Paris–Sorbonne University Hospital Network ICUs from 8 March 2020, to 28 January 2021 | 90 days, 159 | 51, 72 | VV ECMO and VA ECMO | EOLIA trial respiratory severity criteria | 40% hypertension; 34% diabetes; 15% chronic respiratory disease; 6% immunocompromise | 94% neuromuscular blockade; 92% prone positioning; 43% inhaled NO/prostacyclin; 6% high-dose corticosteroids; 0.6% almitrine; 3% renal replacement therapy | From ICU admission to ECMO | | HR 3.02 (1.15–7.92); multivariate adjustment |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shaefi, 2021, USA [61] | Retrospective cohort | data from the STOPCOVID (ICUs at 55 geographically diverse hospitals across the US) between 1 March and 1 July 2020 | Until discharge, death or 1 September 2020 (minimum of 60 days), 190 | 49, 72 | VV ECMO | PaO$_2$/FiO$_2$ ratio < 100 mmHg while receiving IMV | 6.8% chronic lung disease; 3.7% chronic artery disease; 2.1% chronic liver disease; 1.1% end-stage renal disease; 1.6% active malignancy; 62.6% any chronic condition | 78.4% IMV; 71.1% prone positioning; 78.4% neuromuscular blockade; 15.8% inhaled NO; 19% inhaled epoprostenol; 71.6% anticoagulation | From symptom onset to ECMO; From hospital admission to ECMO; From ICU admission to ECMO; From MV to ECMO; ECMO duration | 12.70 ± 4.50; 13.35 ± 6.83; 5.00 ± 3.00; 7.06 ± 5.31; 2.65 ± 3.75; 3.65 ± 3.79; 2.35 ± 3.75; 3.35 ± 3.79; 16.70 ± 10.50; 15.65 ± 9.86 | |
| Supady, 2021, Germany [62] | Retrospective cohort | 15 centers in the US, Germany, Belgium, Switzerland, and Italy from 12 March 2020, through 5, June 2020 | 30 days, 127 | 59, 79 | VV ECMO | NA | 2% heart failure NYHA IV; 10% chronic lung disease; 9% dialysis-dependent kidney failure; 5% hematologic malignancy; 2% solid malignant tumor; 6% immunosuppressive therapy | 74% prone positioning before ECMO; 5% NO use; 9% bicarbonate use; 53% neuromuscular blockers; 19% renal replacement therapy | From MV to ECMO | 4.06 ± 5.30; 7.06 ± 5.70 | |
| Takeuchi, 2022, Japan [63] | Retrospective cohort | Osaka Prefecture between 29 January and 9 November 2020 | Ended on the day of ECMO termination of died, 39 | NA, 92 | NA | NA | 41% comorbidities | NA | From symptom onset to ECMO; ECMO duration | 14.00 ± 6.29; 11.64 ± 4.12; 14.64 ± 7.08; 9.64 ± 9.06 | |
| Trejnowska, 2022, Poland [64] | Retrospective cohort | four Polish ECMO centers between 1 March 2020, and 31 May 2021 | NA, 158 | 46, 75 | Mainly VV ECMO | persistent hypoxemia with PaO$_2$/FiO$_2$ < 150 mmHg and/or respiratory acidosis with pH < 7.25 and PaCO$_2$ > 60 mmHg | 25.9% arterial hypertension; 7% chronic pulmonary disease; 2.5% cancer; 4.4% psychiatric disorders; 3.8% thyroid dysfunction; 12.7% diabetes; 1.9% chronic heart failure; 3.8% CAD; | NA | From hospital admission to ECMO; From MV to ECMO | 6.30 ± 5.70; 8.10 ± 6.10; 4.80 ± 5.20; 5.60 ± 6.50 | |
| Varghese, 2021, USA [65] | Retrospective cohort | MedStar Washington Hospital Center from April 2020 through December 2020 | NA, 32 | 45, 69 | VV ECMO | NA | 62.5% hypertension; 37.5% diabetes | NA | From symptom onset to ECMO; From hospital admission to ECMO; From MV to ECMO | 18.00 ± 5.70; 12.00 ± 7.00; 5.57 ± 6.21; 3.92 ± 5.61; 5.86 ± 4.35; 3.78 ± 4.00 | |
| Vigneshwar, 2022, USA [66] | Prospective cohort | 4 ECMO referral centers between March and October 2020 | NA, 51 | 50, 65 | VV ECMO | International ELSO guidelines | 5.88% COPD; 39.21% essential hypertension; 39.21% diabetes; 50.98% peripheral artery disease; 3.92% stroke/transient ischemic attack; 19.61% asthma; 7.84% central nervous system dysfunction | 29.41% inotrope; 37.25% steroids; 21.57% cytokine blocker; 52.94% remdesivir; 35.29% hydrochloroquine/chloroquine; 60.78% convalescent plasma | ECMO duration | 12.42 ± 7.76; 18.08 ± 10.41 | |
| Yang, 2020, China [67] | Retrospective cohort | Twenty-one ICUs in Hubei since 1 January | Up to 31 May 2020 73 | 60, 63 | VV ECMO | NA | 13.7% CAD; 37% hypertension; 17.8% diabetes; 6.8% COPD; 1.4% malignancy | 23.7% renal replacement therapy; 66.1% prone position ventilation; 86.4% steroid therapy; 11.8% convalescent plasma | From symptom to ECMO; From MV to ECMO | 24.00 ± 8.24; 24.41 ± 10.64; 2.59 ± 4.94; 4.00 ± 4.56 | |
| Yaqoob, 2022, USA [68] | Retrospective cohort | The ICUs of a quaternary care hospital between 3 January 2020 and 31 August 2021 | NA, 31 | 47, 65 | NA | NA | NA | NA | From MV to ECMO | 2.92 ± 3.82; 4.86 ± 5.19 | |
| Yoshino, 2021, Japan [69] | Retrospective cohort | Fukuoka University Hospital ECMO Center between April 2020 and December 2020 | NA, 19 | 61, 84 | NA | NA | NA | NA | ECMO duration | 8.18 ± 5.45; 40.81 ± 56.95 | |
| Zaaqoq, 2022, USA [70] | Retrospective cohort | quaternary care institution from 1 April 2020, to 1 January 2021 | NA, 32 | 44, 69 | VV ECMO | EOLIA trial criteria | 46.9% obesity; 37.5% diabetes; 34.4% hypertension; 3.1% malignancy | 31.25% hydroxychloroquine; 28.13% azithromycin; 40.6% IL-6 inhibitor; 15.6% intravenous steroids; 33.3% remdesivir; 21.9% convalescent plasma | From symptom onset to ECMO; From MV to ECMO; ECMO duration | 15.55 ± 6.47; 9.73 ± 8.18; 2.64 ± 2.43; 2.45 ± 3.27; 12.00 ± 15.88; 22.09 ± 23.72 | |

**Table 1.** *Cont.*

| Author, Year, Country | Study Design | Data Source | Follow-Up Time, Sample Size | Mean Age (Years), Male (%) | ECMO Type | ECMO Initiation | Pre-ECMO Baseline Comorbidities | Other Treatment | Time Period | Survivor and Non-Survivor Time (Mean ± Standard Deviation; Day) | Estimate Effect (95% CI) and Ad-justed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zayat, 2021, Germany [71] | Retrospective cohort | RWTH Aachen University Hospital from 1 March 2020, to 20 April 2020 | NA, 17 | 57, 65 | VV ECMO and VA ECMO | ELSO | 35% hypertension; 6%CAD; 35% diabetes; 82% kidney disease; 6% peripheral arterial disease; 29% prior pneumonia; 18% COPD; 35% atrial fibrillation; 6% malignancy | 18% antiviral treatment; 70.6% inotropes; 88.2% vasopressor; 47% inhaled NO inhalation | From hospital admission to ECMO / From MV to ECMO / ECMO duration | 4.00 ± 1.75; 11.81 ± 12.06 / 3.37 ± 0.87; 9.25 ± 13.40 / 15.26 ± 7.00; 15.44 ± 11.17 | |
| Zhang, 2020, UK [72] | Retrospective cohort | GSTFT in London between 3 March and 2 May 2020 | NA, 43 | 45, 77 | VV ECMO | NA | 48.8% obesity; 23.3% hypertension; 18.6% diabetes; 11.6% asthma | NA | From MV to ECMO / ECMO duration | 4.29 ± 3.12; 3.64 ± 4.12 / 14.36 ± 10.14; 12.05 ± 10.09 | |

Abbreviations: ECMO: extracorporeal membrane oxygenation; USA: the United States of America; VV: venovenous; VA: venoarterial; ELSO: Extracorporeal Life Support Organization; AKI: acute kidney injury; IL: interleukin; ICU: intensive care unit; EOLIA: ECMO to Rescue Lung Injury in Severe ARDS; VAV: venoarterio-venous; $FiO_2$: fraction of inspiration $O_2$; PEEP: positive end-expiratory pressure; VT: tidal volume; ml: milliliter; kg: kilogram; PBW: predicted body weight; $PaO_2$: partial pressure of oxygen; mmHg: millimeter of mercury; pH: hydrogen ion concentration; $PaCO_2$: partial pressure of carbon dioxide; RR: respiratory rate; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CKD: chronic kidney disease; HR: hazard ratio; UK: United Kingdom of Great Britain and Northern Ireland; VVA: veno-venoarterial; NA: not available; MV: mechanical ventilation; OR: odds ratio; BMI: body mass index; PRESERVE: PRedicting dEath for SEvere ARDS on veno-venous ECMO; IMV: invasive mechanical ventilation; SAPS: simplified acute physiology score; NO: nitric oxide; SCOPE: SpecialtyCare Operative Procedural rEgistry; US: United States; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; ARDS: acute respiratory distress syndrome; ARNI: angiotensin receptor neprilysin inhibitor; COVID-19: coronavirus disease 2019; ECMOSARS: The Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome Coronavirus 2; NSAID: nonsteroidal anti-inflammatory drug; SWAAC-ELSO: The South Asia, West Asia, and Africa Chapter of Extracorporeal Life Support Organization; RR: relative risk; STOPCOVID: Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19; NYHA II: New York Heart Association II; GSTFT: Guy's and St Thomas' NHS Foundation Trust.

### 3.3. Quality Evaluation

Of the fifty-four included articles, five studies had an NOS score of five [51,63,65,68,69], and twenty-three had a score of six [20,24–27,32,35,38,40,43–48,50,52,64,66,67,70–72]. Effect sizes and follow-up times were not reported, raising concerns about selection and outcome bias. The remaining studies were all of high quality, with a score of more than six (Supplementary Table S4).

### 3.4. Baseline Differences and Meta-Analysis of Pre-ECMO Time in COVID-19 Patients' Survival

#### 3.4.1. Time from Symptom Onset to ECMO

Fifteen articles with 475 survivors and 472 non-survivors showed differences in the time from symptom onset to ECMO [4,24,26,31,39,40,42,50,54,55,61,63,65,67,70]. There was no time difference between survivors and non-survivors (SMD = −0.17, 95% CI: [−0.41, 0.07], $p$ = 0.15; $I^2$ = 58%, $p$ = 0.003) (Figure 2a).

a. Difference between survivors and non-survivors
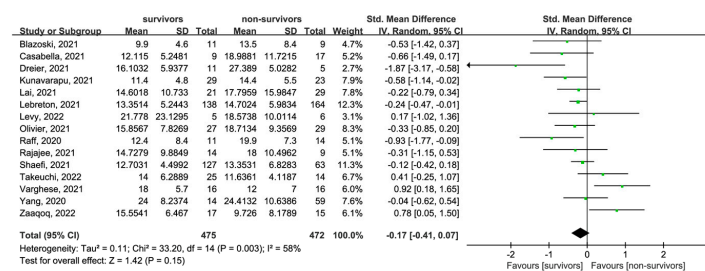


b. Per 1 day increase
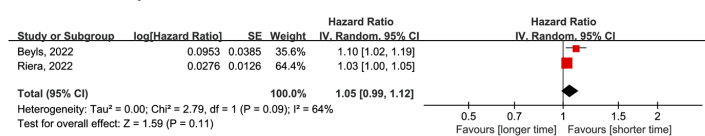


**Figure 2.** Forest plot for the association between time from symptom onset to ECMO and survival in COVID-19 patients. (**a**). Forest plot showing the time differences between survivors and non-survivors in COVID-19 patients. (**b**). Forest plot for the association between time and survival, analyzed as continuous variables (per one-day increase).

Two cohort studies, including 373 COVID-19 patients, were used for the analysis of time from symptom onset to ECMO and survival [22,56]. The results showed that there was no significant association between a longer time and the risk of death (HR = 1.05, 95% CI: [0.99, 1.12], $p$ = 0.11; $I^2$ = 64%, $p$ = 0.09) (Figure 2b).

#### 3.4.2. Time from COVID-19 Diagnosis to ECMO

Four cohorts, including 480 survivors and 660 non-survivors, showed the difference in time from COVID-19 diagnosis to ECMO [34,38,47,52]. The result shows that non-survivors had a longer time than survivors (SMD = −0.41, 95% CI: [−0.53, −0.29], $p$ < 0.00001), with low heterogeneity ($I^2$ = 0%, $p$ = 0.39) (Supplementary Figure S1A).

#### 3.4.3. Time from Hospital Admission to ECMO

Analyzing eleven studies (495 survivors and 510 non-survivors) [20,24,25,39,42,46,48,61,64,66,71], non-survivors had a longer time from hospital admission to ECMO than survivors (SMD = −0.53, 95% CI: [−0.97, −0.09], $p$ = 0.02), with high evidence of heterogeneity ($I^2$ = 88%, $p$ < 0.00001) (Supplementary Figure S1B).

#### 3.4.4. Time from ICU Admission to ECMO

Four cohorts with 233 survivors and 176 non-survivors reported the difference in baseline time from ICU admission to ECMO between the two groups [23,29,44,61]. Compared with

survivors, non-survivors had a longer time (SMD = −0.28, 95% CI: [−0.49, −0.08], $p$ = 0.007; $I^2$ = 3%, $p$ = 0.38) (Supplementary Figure S1C).

In addition, Daviet's study showed that there was no association between time from ICU admission to ECMO and survival in COVID-19 patients (OR = 1.175, 95% CI: [0.984, 1.403], $p$ = 0.075) [29]. Instead, Raff's team and Schmidt's team reported that each additional day spent in the ICU prior to ECMO cannulation conferred an adjusted RR of death of 1.04 (95% CI: [1.01, 1.09], $p$ = 0.027) [54], and a longer interval from ICU admission to ECMO tended to be associated with higher 90-day mortality (more than ten days: less than four days HR = 3.02, 95% CI: [1.15, 7.92], $p$ = 0.066), respectively.

### 3.4.5. Time from Intubation or MV to ECMO

Thirty-four cohorts, including 1700 survivors and 1874 non-survivors, showed that the time from intubation or MV to ECMO differed between survivors and non-survivors [19,24,26–30,33–36,38–40,42–45,47,50,52,54,55,57,59,61,62,64,66–68,70–72]. Non-survivors had a longer time from intubation or MV to ECMO than survivors (SMD = −0.21. 95% CI: [−0.32, −0.09], $p$ = 0.0003; $I^2$ = 53%, $p$ = 0.0002) (Supplementary Figure S1D(a)).

Ten studies were pooled to explore the association between time from intubation or MV to ECMO and survival, respectively [30,34,36,37,39,42,51,53,56,58]. Pooled results showed that there was no association between a shorter time and an increased survival in analyses of the highest versus lowest time groups (OR = 1.18, 95% CI: [0.78, 1.78], $p$ = 0.42; $I^2$ = 39%, $p$ = 0.20) (Supplementary Figure S1D(b)) or per one-day increase (OR = 1.14, 95% CI: [0.86, 1.52], $p$ = 0.92; $I^2$ = 90%, $p$ < 0.0001; HR = 0.99, 95% CI: [0.95, 1.02], $p$ = 0.39; $I^2$ = 70%, $p$ = 0.02) (Supplementary Figure S1D(c)). Excluding the Lebreton study [42], we reduced the $I^2$ from 90% to 0%, and the OR became 1.31 (95% CI: [1.14, 1.51], $p$ = 1.00).

### 3.5. Baseline Differences in ECMO Duration in COVID-19 Patients' Survival

Thirty-five articles with thirty-six cohorts (5358 survivors and 6052 non-survivors) reported the difference in ECMO duration between survivors and non-survivors [19–21,23,24,27–29,32–39,41–50,55,57,61,63,66,69–72]. The result showed that non-survivors had a longer ECMO duration compared to survivors (SMD = −0.18, 95% CI: [−0.30, −0.06], $p$ = 0.003; $I^2$ = 81%, $p$ < 0.00001) (Figure 3).
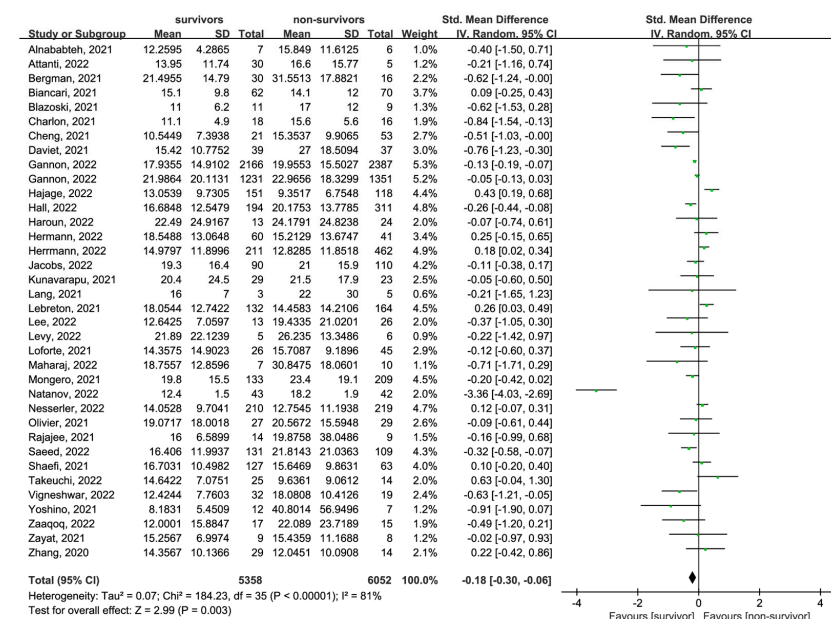


**Figure 3.** Forest plot showing the differences in ECMO duration between survivors and non-survivors in COVID-19 patients. Abbreviations: COVID-19: Coronavirus disease 2019; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; MV: mechanical ventilation.

*3.6. Regression Analysis of Pre-ECMO Time and ECMO Duration*

Twenty-nine studies were involved in the regression analysis [19,20,23,24,27–29,33–36,38,39,42–48,50,55,58,61,63,65,70–72]. The results of the linear regression analysis indicate that the time before ECMO was significantly associated with the duration of ECMO, either in survivors (time from symptom onset to ECMO β = 0.35, 95% CI: [−0.49, 1.19], *p* = 0.37; time from COVID-19 diagnosis to ECMO β = 0.01, 95% CI: [−19.57, 19.60], *p* = 0.99; time from hospital admission to ECMO β = −0.92, 95% CI: [−1.85, 0.01], *p* = 0.051; time from ICU admission to ECMO β = 0.46, 95% CI: [−0.43, 1.34], *p* = 0.16; time from intubation or MV to ECMO β = −0.16, 95% CI: [−0.87, 0.55], *p* = 0.65) or in non-survivors (time from symptom onset to ECMO β = 0.67, 95% CI: [−0.42, 1.76], *p* = 0.19; time from COVID-19 diagnosis to ECMO β = −0.29, 95% CI: [−28.26, 27.67], *p* = 0.92; time from hospital admission to ECMO β = 0.27, 95% CI: [−1.13, 1.68], *p* = 0.66; time from ICU admission to ECMO β = 1.68, 95% CI: [−0.38, 3.74], *p* = 0.07; time from intubation or MV to ECMO β = 0.09, 95% CI: [−0.70, 0.88], *p* = 0.82) (Supplementary Figure S2).

*3.7. Sensitivity Analysis, Subgroup Analysis, and Publication Bias*

We performed a sensitivity analysis for the time from intubation (MV) to ECMO. In the analysis of the OR per one-day increase group, by excluding Lebreton's study, the OR became 1.31 (95% CI: 1.14–1.51). Other sensitivity analyses by deleting one-by-one studies showed consistent results (Supplementary Figure S3). Due to the limited number of included studies (*n* < 10), subgroup and publication bias analyses were not performed according to the guidelines and predefined criteria.

**4. Discussion**

*4.1. Main Finding*

Based on the meta-analysis of 54 studies with 55 cohorts and 13,691 COVID-19 patients, it was found that: (1) non-survival ECMO patients had a longer pre-ECMO time than survivors, including time from COVID-19 diagnosis to ECMO, time from hospital admission to ECMO, time from ICU admission to ECMO, time from intubation or MV use to ECMO, and there was no sufficient evidence to prove the association between pre-ECMO time and COVID-19 survival; (2) there is a longer ECMO time in non-survival COVID-19 patients than survivors; (3) there is no linear relationship between pre-ECMO time and ECMO duration. Although our analysis showed differences in pre-ECMO and ECMO time for survivors versus non-survivors, the relationship between the two needs to be further explored.

The impact of ECMO on the COVID-19 prognosis is significant. The timing and duration of ECMO are significant factors to consider when treating critically ill patients with COVID-19. Previous studies have confirmed that early ECMO intervention after MV improves survival in patients with ARDS caused by influenza A virus subtype H1N1 pneumonia [73]. Most patients with ARDS and severe SARS-CoV-2 pneumonia receive delayed treatment and deteriorate rapidly. Almost all of the studies we included indicated that the pre-ECMO period was shorter in the survival group than in the non-survival group for COVID-19 patients treated with ECMO. Li et al. demonstrated that patients with COVID-19 who received early ECMO treatment had lower mortality than those who received late ECMO treatment [10]. Furthermore, it has been suggested that early use of ECMO may lead to a better prognosis [74], while prolonged ECMO treatment may increase the risk of death and multi-organ failure [75]. A study has shown that an invasive MV duration longer than 7 days before ECMO is a significant prognostic factor for death [76]. Therefore, it is recommended to initiate ECMO as soon as possible [77].

The management of ECMO is also a major factor in the mortality of severe COVID-19 patients. ECMO is classified into three categories based on the route of blood transfusion: veno-venous ECMO (VV-ECMO), venous-arterial ECMO (VA-ECMO), and hybrid ECMO configurations. VV-ECMO provides only respiratory assistance, while VA-ECMO provides both circulatory and respiratory assistance. The choice of ECMO category may impact the patient's prognosis. In critically ill COVID-19 patients, VV-ECMO is the option when

circulatory failure is not present. When circulatory failure is present, such as in the case of refractory hypoxemia associated with ARDS or shock associated with septic cardiomyopathy, VA-ECMO, or hybrid ECMO, is required. Because the use of different ECMOs is not reported in detail in the included literature, we did not perform subgroup analyses for this classification. A meta-analysis was conducted to investigate the effect of exposure to severe hyperoxemia on mortality and neurological outcomes in VA-ECMO-supported patients. The findings showed that exposure to severe hyperoxemia is associated with higher mortality (OR = 1.80, 95% CI: 1.16–2.78) and a poorer neurological outcome (OR = 1.97, 95% CI: 1.30–2.9). Therefore, it is recommended that efforts be made to avoid severe hyperoxemia during VA-ECMO support [78]. In addition, the prolonged use of ECMO increases the chances of nosocomial infections due to COVID-19 infection, which leads to impaired immune function in patients [79,80]. Therefore, it is crucial to improve intubation management. Also, ECMO anticoagulation management needs to pay close attention. Several anticoagulation strategies have been implemented to improve the outcome of COVID-19 patients treated with ECMO. For instance, nafamostat mesylate, a promising anticoagulant drug, could be used for systemic anticoagulation during ECMO administration. It may be able to serve as a feasible and safe option for anticoagulation during ECMO in critically ill patients with COVID-19 [81]. Coagulation tests, such as activated clotting time, should be monitored regularly by healthcare professionals to avoid thrombosis or bleeding [82]. In addition to this, the COVID-19 pandemic has severely strained intensive care resources in hospitals [83]. Although patients may meet the ECMO to Rescue Lung Injury in Severe ARDS trial (EOLIA trial) criteria, ECMO support may not be initiated in time [84,85].

Studies investigating the association between pre-ECMO and ECMO duration and survival in COVID-19 patients have produced inconsistent results. After multifactorial adjustment, Nesserler et al. reported a higher mortality rate with longer pre-ECMO duration (HR = 1.74, 95% CI: 1.07–2.83) [49], while Saeed et al. did not reach the same conclusion (HR = 1.01, 95% CI: 0.98–1.03) [57]. Our results indicated a difference in pre-ECMO time (e.g., MV or time to intubation to ECMO) between COVID-19 survivors and non-survivors, but this time is not statistically related to COVID-19 survival. It is important to note that the limited number of studies may have biased these results. Therefore, caution is advised when interpreting these findings, and further studies are needed to validate the relationship between ECMO-related time and the survival of critically ill COVID-19 patients. In addition, the inconsistency of the two statistical methods introduced some bias. As we are unable to adjust for all confounding factors, only survival and non-survival were considered when combining for time. Instead, in conducting research on the relationship between them, multifactor-adjusted studies were included, in which they adjusted for confounders such as age, comorbidity, type of ECMO, Respiratory ECMO Survival Prediction (RESP) score, and sequential organ failure assessment (SOFA) score, which was the main reason for the inconsistent results. In addition, we included studies for both univariate and multivariate analyses, and due to the limited number of included articles, we were unable to separately analyze studies adjusted for confounding factors. The effect of confounding factors on outcomes still needs to be elucidated.

It is also worth discussing whether the timing of pre-ECMO has an impact on the timing of ECMO. According to our results, in either survivors or non-survivors, pre-ECMO time showed no linear relationship with ECMO duration. In combination with previous relevant clinical studies and the recommendations of the ELSO, the timing of ECMO should be considered when the patient is at or above 50% risk of death in reference to any cause of hypoxic respiratory failure, and ECMO treatment should be initiated when the patient is at or above 80% risk of death. Currently, ECMO is only used as a supportive tool to allow time for primary disease treatment, rather than as a treatment in itself. Early use of ECMO can prevent cellular damage to organs and tissues caused by hypoxic metabolism and provide a favorable opportunity to treat the primary disease. Therefore, the duration of ECMO use is closely related to the improvement of the primary disease. That is, the duration of ECMO use may be shortened if earlier use of ECMO provides more adequate

time to better support the treatment of the primary morbidity and if the primary morbidity improves during ECMO use. In contrast, a shorter duration of pre-ECMO does not mean a shorter duration of ECMO if the primary morbidity is not controlled. Although the early use of ECMO in severe COVID-19 patients is supported, there are no more studies that clearly show a relationship between pre-ECMO and the duration of ECMO use, and this issue still requires ongoing attention.

### 4.2. Underlying Mechanism

The impact of initiating ECMO early on patients with severe COVID-19 is multifactorial. Firstly, it is important to note that ARDS in COVID-19 patients aligns with the Berlin definition [86]. However, Gattinoni et al. proposed an alternative perspective, suggesting that lung compliance is significantly reduced in COVID-19 patients and that severe hypoxemia is more commonly associated with ventilation/perfusion (VA/Q) mismatch. For patients with COVID-19, conventional treatments such as mechanical ventilation or prone ventilation do not improve oxygenation by recruiting collapsed areas [87]. Therefore, early use of ECMO can benefit patients by minimizing ventilator-induced lung injury. Secondly, it has been found that death from COVID-19 is closely linked to hypercoagulable and thrombotic states, as supported by Yin et al. According to their report, platelet levels are higher in COVID-19 patients than in non-COVID-19 pneumonia patients [88]. When administering ECMO cannulation, a systemic anticoagulation strategy is typically employed to ensure safety [89]. Also, the ELSO guideline proposes to consider anticoagulation therapy targeting the higher end of normal for ven-venous ECMO in COVID-19 patients due to their known hypercoagulable state [6]. This approach reduces the risk of thrombosis and subsequent death resulting from the intrinsic thrombotic state, providing an additional benefit to severe COVID-19 patients. Thirdly, hospital-acquired infections are more prevalent in hospitals than in other settings. Prolonged use of ECMO is associated with an increased risk of nosocomial infections [90], which may contribute to mortality.

### 4.3. Clinical Implications

Neither the clinical guidelines related to COVID-19 published by the WHO [91] nor the regularly updated guidelines of the National Institutes of Health [92] take a positive position on whether to apply ECMO to patients with severe COVID-19. However, according to the EOLIA trial, the ELSO made a standard recommendation that ECMO therapy could be used in certain patients with COVID-19 [6]. Subsequently, the Korean Society for Thoracic and Cardiovascular Surgery (KSTCVS) [93] and Chinese experts [94–96] have also recommended ECMO as a salvage therapy for patients with severe COVID-19 who have not responded to conventional ARDS therapy.

Our results show a significant difference between COVID-19 survivors and non-survivors in terms of pre-ECMO time and ECMO duration. This suggests that by adjusting the timing of ECMO, there may be an impact on the survival of patients with severe COVID-19. However, our study failed to identify an association between pre-ECMO and ECMO timing and the survival of COVID-19 patients. Therefore, additional studies and more articles are required to confirm the relationship between ECMO timing and survival in patients with COVID-19, to determine the optimal timing and duration of ECMO treatment for COVID-19, and thus to improve survival in severe COVID-19 patients. In the meantime, further guideline updates or clinical trials may highlight the differences in ECMO-related time in COVID-19 patients and will still require our continued attention.

In addition, it is worth noting that prior treatment with ECMO is crucial for patients with severe COVID-19. Non-invasive respiratory support has been shown to reduce the need for intubation and invasive MV [60], but mortality may be increased in patients with COVID-19 who fail non-invasive ventilation strategies [97,98]. Indeed, dysregulated spontaneous breathing, associated with wide transpulmonary pressure swings, may increase the risk of harmful "patient spontaneous induced lung injury" on non-invasive MV or high-flow nasal cannula therapy, leading to a greater susceptibility to pneumonia and

fibrosis [99,100]. Also, based on existing studies, emergency tracheal intubation and MV are required for severe COVID-19 patients exhibiting signs of respiratory distress, hypoxemia, or encephalopathy. A previous meta-analysis demonstrated that a longer duration of invasive MV was associated with a poor prognosis [101]. Patients who remain unsuccessful after optimization of MV strategies may be considered for pulmonary resuscitation strategies. While invasive MV can benefit patients, it can also cause ventilator-associated lung injury if not used properly. This can be caused by high driving pressure, which has been linked to increased mortality in severe cases of COVID-19.

A study has shown that the prone position can relieve atelectasis even at low positive end-expiratory pressure (PEEP) levels [102]. In patients with severe hypoxia, the prone position can be considered an operation to preserve PEEP. Thus, the prone-position strategy can balance the adverse effects of invasive MV [30]. At the same time, the prone position can improve oxygenation in patients with prolonged hypoxemia during ECMO. When using lung-protective ventilation to reduce lung injury, the addition of prone position therapy in conjunction with ECMO can further aid and optimize alveolar recovery. This combination of strategies (ECMO and prone position) has been shown to improve overall survival [103]. It is also important to consider potential complications when applying the combined strategy, such as accidental decannulation and kinking of the infusion system due to the prone position, as well as coagulation disorders and pressure ulcers.

### 4.4. Comparison with Prior Meta-Analysis

Previous meta-analyses have compared the effect of the presence or absence of ECMO use on COVID-19 mortality or the difference in mortality between COVID-19 and other virus-induced diseases treated with ECMO [7,77,104–106]. For example, Kusumawardhani's study found a significantly higher incidence of mortality in COVID-19 patients treated with ECMO compared to those not treated with ECMO (OR = 15.79, 95% CI: 4.21–59.28, $p$ < 0.0001) [106]. Ramanathan's meta-analysis reported an in-hospital ECMO mortality rate of 37.1% for COVID-19 patients, which is similar to that of patients with non-COVID-19-related ARDS [7].

Currently, no studies have summarized the effect of pre-ECMO and ECMO duration on mortality in COVID-19 patients. Our meta-analysis is the first study based on this. We analyzed pre-ECMO and ECMO timing in COVID-19 survivors versus non-survivors, as well as the association between the ECMO-related time and COVID-19 survival. In addition, we sought to explore the relationship between pre-ECMO time and ECMO time in patients with COVID-19. Although no robust and definitive results were obtained, our study gives direction for future research.

### 4.5. Strength and Limitation

Our study is the first to investigate the relationship between ECMO duration and survival in patients with severe COVID-19. First, we conducted a comprehensive analysis of relevant literature without language restrictions, focusing on a specific and exclusive population. Second, we explored the relationship between ECMO duration and death in COVID-19 patients in two ways: by using continuous variables to explore time-specific differences and by analyzing adjusted effect size to explore associations between the two. Finally, although our study did not demonstrate a causal relationship between ECMO time and survival in ill COVID-19 patients, the difference in ECMO time between the surviving and dying populations could still suggest relevant studies for the following investigations.

Several limitations in our meta-analysis should be noted. First, relatively high heterogeneity was observed in our results. This may be due to the fact that our analysis was based on cohort studies. We included studies with both univariate and multivariate analyses, whose unadjusted confounders may have influenced our results. Second, despite the inclusion of a large number of studies, only a few articles reported effect sizes for the relationship between pre-ECMO or ECMO time and COVID-19 survival ($n$ = 15). And the time periods varied across the studies we included, resulting in a small number of studies

being included in each period (time from intubation or MV to ECMO = 3 for categorical variables and 7 for continuous variables). This may be another cause of bias and inaccurate results. In addition, the studies included in this analysis reported different effect sizes (OR, RR, and HR), making it impossible to report the pooled results due to differences in statistical methodology. It is important to continue to pay attention to relevant research and refine each analysis as needed in the future. Third, out of the 54 studies included, the majority were conducted in America. However, due to the limited number of studies included, subgroup analysis could not be conducted. Hence, the potential influence of confounding and potential intermediate factors, such as regional differences, study design, follow-up, and other clinical characteristics across studies, needs further investigation. Fourth, there were differences in the indicators for ECMO initiation in each study, with some studies following ELSO guidelines and others relying on decisions made by local experts, which may have impacted the results. Fifth, the varying definitions of death in each study and the inconsistent timing of these definitions, coupled with the short-term follow-up periods in most studies, may have led to an underestimation of reported mortality. Sixth, due to the observational nature of the analyses we included and the limited number of articles included, trial sequential analysis was not performed to assess the robustness of the findings and the need for further research. Finally, the meta-analysis is based on observational studies, so causality cannot be deduced from our study.

## 5. Conclusions

Based on current evidence, our results suggest that there are differences in pre-ECMO between COVID-19 survivors and non-survivors. We did not have sufficient evidence of a significant association between pre-ECMO time and survival in COVID-19 patients. In addition, non-survivors had a longer ECMO duration than survivors. Pre-ECMO time does not affect the timing of ECMO. Considering the limited evidence and possible bias, further studies in pre-ECMO and ECMO time on the survival of COVID-19 patients are needed to explore the association between them. Future guidelines may emphasize ECMO timing-specific risk assessment and management for severe COVID-19.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Conflicts of Interest:** The authors declare no competing financial interests.

# References

1. Xie, J.; Wu, W.; Li, S.; Hu, Y.; Hu, M.; Li, J.; Yang, Y.; Huang, T.; Zheng, K.; Wang, Y.; et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: A retrospective multicenter study. *Intensive Care Med.* **2020**, *46*, 1863–1872. [CrossRef] [PubMed]
2. Xu, J.; Yang, X.; Yang, L.; Zou, X.; Wang, Y.; Wu, Y.; Zhou, T.; Yuan, Y.; Qi, H.; Fu, S.; et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: A multicenter ret-rospective study from Wuhan, China. *Crit. Care* **2020**, *24*, 394. [CrossRef] [PubMed]
3. Wu, Z.; McGoogan, J.M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* **2020**, *323*, 1239–1242. [CrossRef] [PubMed]
4. Arabi, Y.M.; Al-Omari, A.; Mandourah, Y.; Al-Hameed, F.; Sindi, A.A.; Alraddadi, B.; Shalhoub, S.; Almotairi, A.; Al Khatib, K.; Abdulmomen, A.; et al. Critically ill Patients with the Middle East Respiratory Syndrome: A Multicenter Retrospective Cohort Study. *Crit. Care Med.* **2017**, *45*, 1683–1695. [CrossRef] [PubMed]
5. Grasso, S.; Terragni, P.; Birocco, A.; Urbino, R.; Del Sorbo, L.; Filippini, C.; Mascia, L.; Pesenti, A.; Zangrillo, A.; Gattinoni, L.; et al. ECMO criteria for influenza A (H1N1)-associated ARDS: Role of transpulmonary pressure. *Intensive Care Med.* **2012**, *38*, 395–403. [CrossRef] [PubMed]
6. Badulak, J.; Antonini, M.V.; Stead, C.M.; Shekerdemian, L.; Raman, L.; Paden, M.L.; Agerstrand, C.; Bartlett, R.H.; Barrett, N.; Combes, A.; et al. Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization. *ASAIO J.* **2021**, *67*, 485–495. [CrossRef] [PubMed]
7. Ramanathan, K.; Shekar, K.; Ling, R.R.; Barbaro, R.P.; Wong, S.N.; Tan, C.S.; Rochwerg, B.; Fernando, S.M.; Takeda, S.; MacLaren, G.; et al. Extracorporeal membrane oxygenation for COVID-19: A systematic review and meta-analysis. *Crit. Care* **2021**, *25*, 211. [CrossRef]
8. Barbaro, R.P.; MacLaren, G.; Boonstra, P.S.; Combes, A.; Agerstrand, C.; Annich, G.; Diaz, R.; Fan, E.; Hryniewicz, K.; Lorusso, R.; et al. Extracorporeal membrane oxygenation for COVID-19: Evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* **2021**, *398*, 1230–1238. [CrossRef]
9. Barbaro, R.P.; MacLaren, G.; Boonstra, P.S.; Iwashyna, T.J.; Slutsky, A.S.; Fan, E.; Bartlett, R.H.; Tonna, J.E.; Hyslop, R.; Fanning, J.J.; et al. Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* **2020**, *396*, 1071–1078. [CrossRef]
10. Li, X.; Hu, M.; Zheng, R.; Wang, Y.; Kang, H.; Jiang, L.; Zhong, M.; Sang, L.; Zheng, X.; Pan, C.; et al. Delayed Initiation of ECMO Is Associated with Poor Outcomes in Patients with Severe COVID-19: A Multicenter Retrospective Cohort Study. *Front. Med.* **2021**, *8*, 716086. [CrossRef]
11. Mathilde, N.; Bérénice, P.; Dorothée, V.; Radj, C.; Laurence, D.; Julien, J.; Eric, B.; Alexandru, N.; Jérôme, A.; Nicolas, A.; et al. Late venovenous extracorporeal membrane oxygenation in patients with acute respiratory distress syndrome due to SARS-CoV-2. *Ann. Intensive Care* **2022**, *12*, 54. [CrossRef]
12. Schuch, F.B.; Vancampfort, D.; Firth, J.; Rosenbaum, S.; Ward, P.B.; Silva, E.S.; Hallgren, M.; Ponce De Leon, A.; Dunn, A.L.; Deslandes, A.C.; et al. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *Am. J. Psychiatry* **2018**, *175*, 631–648. [CrossRef] [PubMed]
13. Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* **2010**, *25*, 603–605. [CrossRef] [PubMed]
14. Luo, D.; Wan, X.; Liu, J.; Tong, T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat. Methods Med. Res.* **2018**, *27*, 1785–1805. [CrossRef] [PubMed]
15. McGrath, S.; Zhao, X.; Steele, R.; Thombs, B.D.; Benedetti, A. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat. Methods Med. Res.* **2020**, *29*, 2520–2537. [CrossRef] [PubMed]
16. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol.* **2014**, *14*, 135. [CrossRef]
17. Simon, S.D. Understanding the odds ratio and the relative risk. *J. Androl.* **2001**, *22*, 533–536. [CrossRef] [PubMed]
18. Higgins, J.P.; Green, S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 [Updated March 2017]*; The Cochrane Collaboration: Melbourne, Australia, 2017. [CrossRef]
19. Akkanti, B.; Suarez, E.E.; O'Neil, E.R.; Rali, A.S.; Hussain, R.; Dinh, K.; Tuazon, D.M.; MacGillivray, T.E.; Diaz-Gomez, J.L.; Simpson, L.; et al. Extracorporeal Membrane Oxygenation for COVID-19: Collaborative Experience from the Texas Medical Center in Houston with 2 Years Follow-up. *ASAIO J.* **2022**, *68*, 1443–1449. [CrossRef]
20. Alnababteh, M.; Hashmi, M.D.; Vedantam, K.; Chopra, R.; Kohli, A.; Hayat, F.; Kriner, E.; Molina, E.; Pratt, A.; Oweis, E.; et al. Extracorporeal membrane oxygenation for COVID-19 induced hypoxia: Single-center study. *Perfusion* **2021**, *36*, 564–572. [CrossRef]

21. Bergman, Z.R.; Wothe, J.K.; Alwan, F.S.; Lofrano, A.E.; Tointon, K.M.; Doucette, M.; Bohman, J.K.; Saavedra-Romero, R.; Prekker, M.E.; Lusczek, E.R.; et al. Risk Factors of Mortality for Patients Receiving Venovenous Extracorporeal Membrane Oxygenation for COVID-19 Acute Respiratory Distress Syndrome. *Surg. Infect.* **2021**, *22*, 1086–1092. [CrossRef]

22. Beyls, C.; Huette, P.; Viart, C.; Mestan, B.; Haye, G.; Guilbart, M.; Bernasinski, M.; Besserve, P.; Leviel, F.; Witte Pfister, A.; et al. Mortality of COVID-19 Patients Requiring Extracorporeal Membrane Oxygenation during the Three Epidemic Waves. *ASAIO J.* **2022**, *68*, 1434–1442. [CrossRef] [PubMed]

23. Biancari, F.; Mariscalco, G.; Dalén, M.; Settembre, N.; Welp, H.; Perrotti, A.; Wiebe, K.; Leo, E.; Loforte, A.; Chocron, S.; et al. Six-Month Survival after Extracorporeal Membrane Oxygenation for Severe COVID-19. *J. Cardiothorac. Vasc. Anesth.* **2021**, *35*, 1999–2006. [CrossRef] [PubMed]

24. Blazoski, C.; Baram, M.; Hirose, H. Outcomes of extracorporeal membrane oxygenation in acute respiratory distress syndrome due to COVID-19: The lessons learned from the first wave of COVID-19. *J. Card Surg.* **2021**, *36*, 2219–2224. [CrossRef]

25. Braaten, J.A.; Bergman, Z.R.; Wothe, J.K.; Lofrano, A.E.; Matzek, L.J.; Doucette, M.; Saavedra-Romero, R.; Bohman, J.K.; Prekker, M.E.; Lusczek, E.R.; et al. Increasing Mortality in Venovenous Extracorporeal Membrane Oxygenation for COVID-19-Associated Acute Respiratory Distress Syndrome. *Crit. Care Explor.* **2022**, *4*, e0655. [CrossRef] [PubMed]

26. Casabella, C.; Pálizas, F.; Lockhart, C.; Las Heras, M.; Matarrese, A.; Espinoza, L.; Norese, M.; Ivulich, D.; Bisso, I.C. Characteristics and outcomes in extracorporeal membrane oxygenation support in COVID-19 patients: A nationwide cohort-study in Argentina. *ASAIO J.* **2021**, *67*, 15.

27. Charlton, M.; Dashey, S.; Stubbs, A.; Lai, F.Y.; Bird, P.W.; Badhwar, V.; Tang, J.W. Comparing SARS-CoV-2 and influenza A(H1N1)pdm09-infected patients requiring ECMO—A single-centre, retrospective observational cohort experience. *J. Infect.* **2021**, *82*, 84–123. [CrossRef] [PubMed]

28. Cheng, W.; Ma, X.D.; Su, L.X.; Long, Y.; Liu, D.W.; Du, B.; Qiu, H.B.; Guan, X.D.; Chen, D.C.; Kang, Y.; et al. Retrospective Study of Critically Ill COVID-19 Patients With and Without Extracorporeal Membrane Oxygenation Support in Wuhan, China. *Front. Med.* **2021**, *8*, 659793. [CrossRef]

29. Daviet, F.; Guilloux, P.; Hraiech, S.; Tonon, D.; Velly, L.; Bourenne, J.; Porto, A.; Gragueb-Chatti, I.; Bobot, M.; Baumstarck, K.; et al. Impact of obesity on survival in COVID-19 ARDS patients receiving ECMO: Results from an ambispective observational cohort. *Ann. Intensive Care* **2021**, *11*, 157. [CrossRef]

30. Diaz, R.A.; Graf, J.; Zambrano, J.M.; Ruiz, C.; Espinoza, J.A.; Bravo, S.I.; Salazar, P.A.; Bahamondes, J.C.; Castillo, L.B.; Gajardo, A.I.J.; et al. Extracorporeal Membrane Oxygenation for COVID-19-associated Severe Acute Respiratory Distress Syndrome in Chile: A Nationwide Incidence and Cohort Study. *Am. J. Respir. Crit. Care Med.* **2021**, *204*, 34–43. [CrossRef]

31. Dreier, E.; Malfertheiner, M.V.; Dienemann, T.; Fisser, C.; Foltan, M.; Geismann, F.; Graf, B.; Lunz, D.; Maier, L.S.; Müller, T.; et al. ECMO in COVID-19—Prolonged therapy needed? A retrospective analysis of outcome and prognostic factors. *Perfusion* **2021**, *36*, 582–591. [CrossRef]

32. Gannon, W.D.; Stokes, J.W.; Gong, W.; Lindsell, C.J.; Tonna, J.E.; Bacchetta, M.; Rice, T.W.; Semler, M.W.; Casey, J.D. Predicting Mortality for Patients Eligible for Extracorporeal Membrane Oxygenation for COVID-19. *Am. J. Respir. Crit. Care Med.* **2022**, *206*, 628–632. [CrossRef]

33. Hajage, D.; Combes, A.; Guervilly, C.; Lebreton, G.; Mercat, A.; Pavot, A.; Nseir, S.; Mekontso-Dessap, A.; Mongardon, N.; Mira, J.P.; et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome Associated with COVID-19: An Emulated Target Trial Analysis. *Am. J. Respir. Crit. Care Med.* **2022**, *206*, 281–294. [CrossRef] [PubMed]

34. Hall, C.A.; Jacobs, J.P.; Stammers, A.H.; St Louis, J.D.; Hayanga, J.W.A.; Firstenberg, M.S.; Mongero, L.B.; Tesdahl, E.A.; Rajagopal, K.; Cheema, F.H.; et al. Multi-institutional Analysis of 505 Patients With Coronavirus Disease-2019 Supported With Extracorporeal Membrane Oxygenation: Predictors of Survival. *Ann. Thorac. Surg.* **2022**, *114*, 61–68. [CrossRef] [PubMed]

35. Haroun, M.W.; Patel, S.R.; Sims, D.B.; Jorde, U.P.; Goldstein, D.J.; Saeed, O. Characteristics and Outcomes of COVID-19 Patients Supported by Venoarterial or Veno-Arterial-Venous Extracorporeal Membrane Oxygenation. *J. Cardiothorac. Vasc. Anesth.* **2022**, *36*, 2935–2941. [CrossRef] [PubMed]

36. Hermann, M.; Laxar, D.; Krall, C.; Hafner, C.; Herzog, O.; Kimberger, O.; Koenig, S.; Kraft, F.; Maleczek, M.; Markstaller, K.; et al. Duration of invasive mechanical ventilation prior to extracorporeal membrane oxygenation is not associated with survival in acute respiratory distress syndrome caused by coronavirus disease 2019. *Ann. Intensive Care* **2022**, *12*, 6. [CrossRef] [PubMed]

37. Herrmann, J.; Lotz, C.; Karagiannidis, C.; Weber-Carstens, S.; Kluge, S.; Putensen, C.; Wehrfritz, A.; Schmidt, K.; Ellerkmann, R.K.; Oswald, D.; et al. Key characteristics impacting survival of COVID-19 extracorporeal membrane oxygenation. *Crit. Care* **2022**, *26*, 190. [CrossRef]

38. Jacobs, J.P.; Stammers, A.H.; St Louis, J.D.; Hayanga, J.W.A.; Firstenberg, M.S.; Mongero, L.B.; Tesdahl, E.A.; Rajagopal, K.; Cheema, F.H.; Patel, K.; et al. Multi-institutional Analysis of 200 COVID-19 Patients Treated with Extracorporeal Membrane Oxygenation: Outcomes and Trends. *Ann. Thorac. Surg.* **2022**, *113*, 1452–1460. [CrossRef] [PubMed]

39. Kunavarapu, C.; Yeramaneni, S.; Melo, J.; Sterling, R.K.; Huskey, L.C.; Sears, L.; Burch, C.; Rodriguez, S.M.; Habib, P.J.; Triana, F.; et al. Clinical outcomes of severe COVID-19 patients receiving early VV-ECMO and the impact of pre-ECMO ventilator use. *Int. J. Artif. Organs* **2021**, *44*, 861–867. [CrossRef] [PubMed]

40. Lai, W.; Li, S.; Du, Z.; Ma, X.; Lu, J.; Gao, W.D.; Abbott, G.W.; Hu, Z.; Kang, Y. Severe Patients with ARDS with COVID-19 Treated with Extracorporeal Membrane Oxygenation in China: A Retrospective Study. *Front. Med.* **2021**, *8*, 699227. [CrossRef]

41. Lang, C.N.; Zotzmann, V.; Schmid, B.; Berchtold-Herz, M.; Utzolino, S.; Biever, P.; Duerschmied, D.; Bode, C.; Wengenmayer, T.; Staudacher, D.L. Intensive Care Resources and 60-Day Survival of Critically-Ill COVID-19 Patients. *Cureus* **2021**, *13*, e13210. [CrossRef]

42. Lebreton, G.; Schmidt, M.; Ponnaiah, M.; Folliguet, T.; Para, M.; Guihaire, J.; Lansac, E.; Sage, E.; Cholley, B.; Mégarbane, B.; et al. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: A multicentre cohort study. *Lancet Respir. Med.* **2021**, *9*, 851–862. [CrossRef]

43. Lee, S.I.; Kang, D.H.; Ahn, H.J.; Kim, M.J.; Shim, M.S.; Lee, J.E. Age is an important prognostic factor in COVID-19 patients treated with extracorporeal membrane oxygenation. *J. Thorac. Dis.* **2022**, *14*, 3094–3097. [CrossRef]

44. Levy, C.; Dognon, N.; Normandin, S.; Duburcq, T.; Gaudet, A. Assessment of plasma endocan for the prediction of mortality in COVID-19 patients undergoing veno-venous ECMO: A pilot study Evaluación del endocan para la predicción de la mortalidad en pacientes COVID-19 sometidos a ECMO veno-venosa: Un estudio piloto. *Med. Intensiv.* **2022**, *47*, 51–54. [CrossRef]

45. Loforte, A.; Di Mauro, M.; Pellegrini, C.; Monterosso, C.; Pelenghi, S.; Degani, A.; Rinaldi, M.; Cura Stura, E.; Sales, G.; Montrucchio, G.; et al. Extracorporeal Membrane Oxygenation for COVID-19 Respiratory Distress Syndrome: An Italian Society for Cardiac Surgery Report. *ASAIO J.* **2021**, *67*, 385–391. [CrossRef] [PubMed]

46. Maharaj, V.; Alexy, T.; Agdamag, A.C.; Kalra, R.; Nzemenoh, B.N.; Charpentier, V.; Bartos, J.A.; Brunsvold, M.E.; Yannopoulos, D. Right Ventricular Dysfunction is Associated with Increased Mortality in Patients Requiring Venovenous Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019. *ASAIO J.* **2022**, *68*, 772–778. [CrossRef] [PubMed]

47. Mongero, L.B.; Stammers, A.H.; Tesdahl, E.A.; Petersen, C.; Patel, K.; Jacobs, J.P. The Use of Extracorporeal Membrane Oxygenation in COVID-19 Patients with Severe Cardiorespiratory Failure: The Influence of Obesity on Outcomes. *J. Extra-Corpor. Technol.* **2021**, *53*, 293–298. [CrossRef] [PubMed]

48. Natanov, R.; Kunkel, E.R.; Wiesner, O.; Haverich, A.; Wiegmann, B.; Rümke, S.; Kühn, C. Determinants of survival in patients on extracorporeal membrane oxygenation therapy due to severe COVID-19. *Perfusion* **2023**, *38*, 1393–1398. [CrossRef] [PubMed]

49. Nesseler, N.; Fadel, G.; Mansour, A.; Para, M.; Falcoz, P.E.; Mongardon, N.; Porto, A.; Bertier, A.; Levy, B.; Cadoz, C.; et al. Extracorporeal membrane oxygenation for respiratory failure related to COVID-19: A nationwide cohort study. *Anesthesiology* **2022**, *136*, 732–748. [CrossRef] [PubMed]

50. Olivier, P.Y.; Ottavy, G.; Hoff, J.; Auchabie, J.; Darreau, C.; Pierrot, M. Prolonged time from intubation to cannulation in VV-ECMO for COVID-19: Does it really matter? *Crit. Care* **2021**, *25*, 385. [CrossRef] [PubMed]

51. Pacheco, A.; Riera, J.; Bonilla, C.; Mera, A.; Argudo, E.; Vázquez, I.; Fernández, P.; Gallart, E.; Papiol, E.; Sánchez, A.; et al. Risk factors for mortality among patients with COVID-19 needing ECMO: Observational study including 24 patients supported in a high volume center with an ICU-based ECMO program. *ASAIO J.* **2020**, *66*, 13.

52. Powell, E.K.; Krause, E.; Esposito, E.; Lankford, A.; Levine, A.; Young, B.A.C.; Haase, D.J.; Tabatabai, A.; Taylor, B.S.; Scalea, T.M.; et al. Time from Infiltrate on Chest Radiograph to Venovenous Extracorporeal Membrane Oxygenation in COVID-19 Affects Mortality. *ASAIO J.* **2023**, *69*, 23. [CrossRef]

53. Rabie, A.A.; Azzam, M.H.; Al-Fares, A.A.; Abdelbary, A.; Mufti, H.N.; Hassan, I.F.; Chakraborty, A.; Oza, P.; Elhazmi, A.; Alfoudri, H.; et al. Implementation of new ECMO centers during the COVID-19 pandemic: Experience and results from the Middle East and India. *Intensive Care Med.* **2021**, *47*, 887–895. [CrossRef] [PubMed]

54. Raff, L.A.; Gallaher, J.R.; Johnson, D.; Raff, E.J.; Charles, A.G.; Reid, T.S. Time to Cannulation after ICU Admission Increases Mortality for Patients Requiring Veno-Venous ECMO for COVID-19 Associated Acute Respiratory Distress Syndrome. *Ann. Surg.* **2022**, *276*, e659. [CrossRef] [PubMed]

55. Rajajee, V.; Fung, C.M.; Seagly, K.S.; Park, P.K.; Raghavendran, K.; Machado-Aranda, D.A.; Scott, J.W.; Delano, M.J.; Abou El Ela, A.; Haft, J.W.; et al. One-Year Functional, Cognitive, and Psychological Outcomes Following the Use of Extracorporeal Membrane Oxygenation in Coronavirus Disease 2019: A Prospective Study. *Crit. Care Explor.* **2021**, *3*, e0537. [CrossRef] [PubMed]

56. Riera, J.; Alcántara, S.; Bonilla, C.; Fortuna, P.; Blandino Ortiz, A.; Vaz, A.; Albacete, C.; Millán, P.; Ricart, P.; Boado, M.V.; et al. Risk factors for mortality in patients with COVID-19 needing extracorporeal respiratory support. *Eur. Respir. J.* **2022**, *59*, 2102463. [CrossRef] [PubMed]

57. Saeed, O.; Stein, L.H.; Cavarocchi, N.; Tatooles, A.J.; Mustafa, A.; Jorde, U.P.; Alvarez, C.; Gluck, J.; Saunders, P.; Abrol, S.; et al. Outcomes by cannulation methods for venovenous extracorporeal membrane oxygenation during COVID-19: A multicenter retrospective study. *Artif. Organs* **2022**, *46*, 1659–1668. [CrossRef] [PubMed]

58. Saeed, O.; Tatooles, A.J.; Farooq, M.; Schwartz, G.; Pham, D.T.; Mustafa, A.K.; D'Alessandro, D.; Abrol, S.; Jorde, U.P.; Gregoric, I.D.; et al. Characteristics and outcomes of patients with COVID-19 supported by extracorporeal membrane oxygenation: A retrospective multicenter study. *J. Thorac. Cardiovasc. Surg.* **2022**, *163*, 2107–2116.e2106. [CrossRef] [PubMed]

59. Schmidt, M.; Hajage, D.; Lebreton, G.; Monsel, A.; Voiriot, G.; Levy, D.; Baron, E.; Beurton, A.; Chommeloux, J.; Meng, P.; et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: A retrospective cohort study. *Lancet Respir. Med.* **2020**, *8*, 1121–1131. [CrossRef] [PubMed]

60. Schmidt, M.; Langouet, E.; Hajage, D.; James, S.A.; Chommeloux, J.; Bréchot, N.; Barhoum, P.; Lefèvre, L.; Troger, A.; de Chambrun, M.P.; et al. Evolving outcomes of extracorporeal membrane oxygenation support for severe COVID-19 ARDS in Sorbonne hospitals, Paris. *Crit. Care* **2021**, *25*, 355. [CrossRef]

61. Shaefi, S.; Brenner, S.K.; Gupta, S.; O'Gara, B.P.; Krajewski, M.L.; Charytan, D.M.; Chaudhry, S.; Mirza, S.H.; Peev, V.; Anderson, M.; et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med.* **2021**, *47*, 208–221. [CrossRef] [PubMed]

62. Supady, A.; DellaVolpe, J.; Taccone, F.S.; Scharpf, D.; Ulmer, M.; Lepper, P.M.; Halbe, M.; Ziegeler, S.; Vogt, A.; Ramanan, R.; et al. Outcome Prediction in Patients with Severe COVID-19 Requiring Extracorporeal Membrane Oxygenation—A Retrospective International Multicenter Study. *Membranes* **2021**, *11*, 170. [CrossRef] [PubMed]

63. Takeuchi, T.; Zha, L.; Tanaka, K.; Katayama, Y.; Sobue, T.; Hirayama, A.; Komukai, S.; Shimazu, T.; Kitamura, T. Clinical epidemiology and outcomes of COVID-19 patients with extracorporeal membrane oxygenation support in Japan: A retrospective study. *IJID Reg.* **2022**, *3*, 183–188. [CrossRef] [PubMed]

64. Trejnowska, E.; Drobiński, D.; Knapik, P.; Wajda-Pokrontka, M.; Szułdrzyński, K.; Staromłyński, J.; Nowak, W.; Urlik, M.; Ochman, M.; Goździk, W.; et al. Extracorporeal membrane oxygenation for severe COVID-19-associated acute respiratory distress syndrome in Poland: A multicenter cohort study. *Crit. Care* **2022**, *26*, 97. [CrossRef] [PubMed]

65. Varghese, J.; Sallam, T.; Liu, J.; Almasri, M.; Alkordy, Z.; Zaaqoq, A. Effect of symptoms duration on the outcome of COVID-19 patients supported by venovenous extracorporeal membrane oxygenation. *ASAIO J.* **2021**, *67*, 18.

66. Vigneshwar, N.G.; Masood, M.F.; Vasic, I.; Krause, M.; Bartels, K.; Lucas, M.T.; Bronsert, M.; Selzman, C.H.; Thompson, S.; Rove, J.Y.; et al. Venovenous Extracorporeal Membrane Oxygenation Support in Patients with COVID-19 Respiratory Failure: A Multicenter Study. *JTCVS Open* **2022**, *12*, 211–220. [CrossRef] [PubMed]

67. Yang, X.; Hu, M.; Yu, Y.; Zhang, X.; Fang, M.; Lian, Y.; Peng, Y.; Wu, L.; Wu, Y.; Yi, J.; et al. Extracorporeal Membrane Oxygenation for SARS-CoV-2 Acute Respiratory Distress Syndrome: A Retrospective Study from Hubei, China. *Front. Med.* **2020**, *7*, 611460. [CrossRef] [PubMed]

68. Yaqoob, H.; Henson, T.; Greenberg, D.; Peneyra, D.; Huang, L.; Pitaktong, A.; Epelbaum, O.; Chandy, D. Comparison of Extracorporeal Membrane Oxygenation Survivors with Non-Survivors; A Retrospective Analysis at a Quaternary Center. *Am. J. Respir. Crit. Care Med.* **2022**, *205*, A4287. [CrossRef]

69. Yoshino, A.; Nakamura, Y.; Irie, Y.; Kitamura, T.; Takata, T.; Ishikura, H.; Kondo, S. Oral Health of COVID-19 Patients Using Extracorporeal Membrane Oxygenation: A Clinical Study of 19 Cases. *J. Clin. Med.* **2021**, *11*, 42. [CrossRef] [PubMed]

70. Zaaqoq, A.; Sallam, T.; Merley, C.; Galloway, L.A.; Desale, S.; Varghese, J.; Alnababteh, M.; Kriner, E.; Kitahara, H.; Shupp, J.; et al. The Interplay of Inflammation and Coagulation in COVID-19 Patients Receiving Extracorporeal Membrane Oxygenation Support. *Perfusion* **2023**, *38*, 384–392. [CrossRef]

71. Zayat, R.; Kalverkamp, S.; Grottke, O.; Durak, K.; Dreher, M.; Autschbach, R.; Marx, G.; Marx, N.; Spillner, J.; Kersten, A. Role of extracorporeal membrane oxygenation in critically Ill COVID-19 patients and predictors of mortality. *Artif. Organs* **2021**, *45*, E158–E170. [CrossRef]

72. Zhang, J.; Merrick, B.; Correa, G.L.; Camporota, L.; Retter, A.; Doyle, A.; Glover, G.W.; Sherren, P.B.; Tricklebank, S.J.; Agarwal, S.; et al. Veno-venous extracorporeal membrane oxygenation in coronavirus disease 2019: A case series. *ERJ Open Res.* **2020**, *6*, 463–2020. [CrossRef] [PubMed]

73. Sukhal, S.; Sethi, J.; Ganesh, M.; Villablanca, P.; Malhotra, A.; Ramakrishna, H. Extracorporeal membrane oxygenation in severe influenza infection with respiratory failure: A systematic review and meta-analysis. *Ann. Card. Anaesth.* **2017**, *20*, 14–21. [CrossRef] [PubMed]

74. Yang, X.; Cai, S.; Luo, Y.; Zhu, F.; Hu, M.; Zhao, Y.; Zheng, R.; Li, X.; Hu, B.; Peng, Z. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome: A Multicenter Descriptive Study. *Crit. Care Med.* **2020**, *48*, 1289–1295. [CrossRef] [PubMed]

75. Makdisi, G.; Wang, I.-W. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J. Thorac. Dis.* **2015**, *7*, E166–E176.

76. Zeng, Y.; Cai, Z.; Xianyu, Y.; Yang, B.X.; Song, T.; Yan, Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: A retrospective case series. *Crit. Care* **2020**, *24*, 148. [CrossRef]

77. Zhang, Y.; Wang, L.; Fang, Z.X.; Chen, J.; Zheng, J.L.; Yao, M.; Chen, W.Y. Mortality in patients with COVID-19 requiring extracorporeal membrane oxygenation: A meta-analysis. *World J. Clin. Cases* **2022**, *10*, 2457–2467. [CrossRef]

78. Tigano, S.; Caruso, A.; Liotta, C.; LaVia, L.; Vargas, M.; Romagnoli, S.; Landoni, G.; Sanfilippo, F. Exposure to severe hyperoxia worsens survival and neurological outcome in patients supported by veno-arterial extracorporeal membrane oxygenation: A meta-analysis. *Resuscitation* **2023**, *194*, 110071. [CrossRef]

79. Haye, G.; Fourdrain, A.; Abou-Arab, O.; Berna, P.; Mahjoub, Y. COVID-19 Outbreak in France: Setup and Activities of a Mobile Extracorporeal Membrane Oxygenation Team during the First 3 Weeks. *J. Cardiothorac. Vasc. Anesth.* **2020**, *34*, 3493–3495. [CrossRef]

80. Ñamendys-Silva, S.A. ECMO for ARDS due to COVID-19. *Heart Lung* **2020**, *49*, 348–349. [CrossRef]

81. Lang, Y.; Zheng, Y.; Qi, B.; Zheng, W.; Wei, J.; Zhao, C.; Gao, W.; Li, T. Anticoagulation with nafamostat mesilate during extracorporeal life support. *Int. J. Cardiol.* **2022**, *366*, 71–79. [CrossRef]

82. Barbaro, R.P.; Odetola, F.O.; Kidwell, K.M.; Paden, M.L.; Bartlett, R.H.; Davis, M.M.; Annich, G.M. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 894–901. [CrossRef] [PubMed]

83. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W.; Barnaby, D.P.; Becker, L.B.; Chelico, J.D.; Cohen, S.L.; et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA* **2020**, *323*, 2052–2059. [CrossRef] [PubMed]

84. Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Ou, C.Q.; He, J.X.; Liu, L.; Shan, H.; Lei, C.L.; Hui, D.S.C.; et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720. [CrossRef] [PubMed]

85. Yu, Y.; Xu, D.; Fu, S.; Zhang, J.; Yang, X.; Xu, L.; Xu, J.; Wu, Y.; Huang, C.; Ouyang, Y.; et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: A cross-sectional study. *Crit. Care* **2020**, *24*, 219. [CrossRef]

86. Ranieri, V.M.; Rubenfeld, G.D.; Thompson, B.T.; Ferguson, N.D.; Caldwell, E.; Fan, E.; Camporota, L.; Slutsky, A.S. Acute respiratory distress syndrome: The Berlin Definition. *JAMA* **2012**, *307*, 2526–2533. [CrossRef] [PubMed]

87. Gattinoni, L.; Chiumello, D.; Rossi, S. COVID-19 pneumonia: ARDS or not? *Crit. Care* **2020**, *24*, 154. [CrossRef] [PubMed]

88. Yin, S.; Huang, M.; Li, D.; Tang, N. Difference of coagulation features between severe pneumonia induced by SARS-CoV-2 and non-SARS-CoV-2. *J. Thromb. Thrombolysis* **2021**, *51*, 1107–1110. [CrossRef]

89. Fina, D.; Matteucci, M.; Jiritano, F.; Meani, P.; Lo Coco, V.; Kowalewski, M.; Maessen, J.; Guazzi, M.; Ballotta, A.; Ranucci, M.; et al. Extracorporeal membrane oxygenation without therapeutic anticoagulation in adults: A systematic review of the current literature. *Int. J. Artif. Organs* **2020**, *43*, 570–578. [CrossRef]

90. Henry, B.M.; Lippi, G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J. Crit. Care* **2020**, *58*, 27–28. [CrossRef]

91. World Health Organization. *Clinical Management of COVID-19: Interim Guidance*; World Health Organization: Geneva, Switzerland, 2020; Available online: https://iris.who.int/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf?sequence=1 (accessed on 18 August 2023).

92. National Institutes of Health. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*; National Institutes of Health: Bethesda, MA, USA, 2020. Available online: http://www.covid19treatmentguidelines.nih.gov/ (accessed on 31 December 2020).

93. Jeong, I.S.; Kim, W.H.; Baek, J.H.; Choi, C.H.; Choi, C.W.; Chung, E.S.; Jang, J.S.; Jang, W.S.; Jung, H.; Jung, J.S.; et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019: Expert Recommendations from The Korean Society for Thoracic and Cardiovascular Surgery. *J. Chest Surg.* **2021**, *54*, 2–8. [CrossRef]

94. Barrasa, H.; Rello, J.; Tejada, S.; Martín, A.; Balziskueta, G.; Vinuesa, C.; Fernández-Miret, B.; Villagra, A.; Vallejo, A.; San Sebastián, A.; et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 553–561. [CrossRef] [PubMed]

95. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef] [PubMed]

96. Tang, X.; Du, R.-H.; Wang, R.; Cao, T.-Z.; Guan, L.-L.; Yang, C.-Q.; Zhu, Q.; Hu, M.; Li, X.-Y.; Li, Y.; et al. Comparison of Hospitalized Patients with ARDS Caused by COVID-19 and H1N1. *CHEST* **2020**, *158*, 195–205. [CrossRef] [PubMed]

97. Kang, B.J.; Koh, Y.; Lim, C.M.; Huh, J.W.; Baek, S.; Han, M.; Seo, H.S.; Suh, H.J.; Seo, G.J.; Kim, E.Y.; et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med.* **2015**, *41*, 623–632. [CrossRef] [PubMed]

98. Valley, T.S.; Walkey, A.J.; Lindenauer, P.K.; Wiener, R.S.; Cooke, C.R. Association between Noninvasive Ventilation and Mortality among Older Patients with Pneumonia. *Crit. Care Med.* **2017**, *45*, e246–e254. [CrossRef] [PubMed]

99. Brochard, L. Ventilation-induced lung injury exists in spontaneously breathing patients with acute respiratory failure: Yes. *Intensive Care Med.* **2017**, *43*, 250–252. [CrossRef] [PubMed]

100. Brochard, L.; Slutsky, A.; Pesenti, A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 438–442. [CrossRef] [PubMed]

101. Tran, A.; Fernando, S.M.; Rochwerg, B.; Barbaro, R.P.; Hodgson, C.L.; Munshi, L.; MacLaren, G.; Ramanathan, K.; Hough, C.L.; Brochard, L.J.; et al. Prognostic factors associated with mortality among patients receiving venovenous extracorporeal membrane oxygenation for COVID-19: A systematic review and meta-analysis. *Lancet Respir. Med.* **2023**, *11*, 235–244. [CrossRef]

102. Cornejo, R.A.; Díaz, J.C.; Tobar, E.A.; Bruhn, A.R.; Ramos, C.A.; González, R.A.; Repetto, C.A.; Romero, C.M.; Gálvez, L.R.; Llanos, O.; et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **2013**, *188*, 440–448. [CrossRef]

103. Lucchini, A.; De Felippis, C.; Pelucchi, G.; Grasselli, G.; Patroniti, N.; Castagna, L.; Foti, G.; Pesenti, A.; Fumagalli, R. Application of prone position in hypoxaemic patients supported by veno-venous ECMO. *Intensive Crit. Care Nurs.* **2018**, *48*, 61–68. [CrossRef]

104. Bertini, P.; Guarracino, F.; Falcone, M.; Nardelli, P.; Landoni, G.; Nocci, M.; Paternoster, G. ECMO in COVID-19 Patients: A Systematic Review and Meta-analysis. *J. Cardiothorac. Vasc. Anesth.* **2022**, *36*, 2700–2706. [CrossRef]

105. Elsayed, H.H.; Hassaballa, A.S.; Ahmed, T.A.; Gumaa, M.; Sharkawy, H.Y. Extracorporeal membrane oxygenation (ECMO) in patients with severe COVID-19 adult respiratory distress syndrome: A systematic review and meta-analysis. *Cardiothorac. Surg.* **2021**, *29*, 9. [CrossRef]

106. Kusumawardhani, N.; Dewi, I.P.; Dharmadjati, B.B. Extracorporeal Membrane Oxygenation Used in Acute Respiratory Distress Syndrome with COVID-19: A Systematic Review and Meta-Analysis. *J. Saudi Heart Assoc.* **2021**, *33*, 177–185. [CrossRef]