Extracorporeal Membrane Oxygenation in COVID-19 Patients with Acute Respiratory Disorder Syndrome: Literature Review

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ABSTRACT

Background: COVID-19 is an infectious disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It develops into acute respiratory distress and the majority of affected patients are placed under respiratory assistance in the intensive care unit. Furthermore, several efforts have been made to treat this condition, and these include refractory to mechanical ventilation, and Extracorporeal Membrane Oxygenation (ECMO) therapy following the guidelines recently published by the Extracorporeal Life Support Organization (ELSO). Objectives: This study aims to identify the effectiveness of using ECMO therapy in prolonging the life expectancy of COVID-19 patients with Acute Respiratory Distress Syndrome (ARDS) in the intensive care unit (ICU). Methods: This literature review identified 6 relevant studies following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA). Results: A total of 32 from 157 full-text articles were analyzed based on the eligibility criteria. Meanwhile, up to 6 selected articles were obtained, including 263 for COVID-19 patients that required ECMO therapy in the ICU. A total of 119 were decannulated and discharged from the ICU/hospital, 25 were still being treated with ECMO and 119 died. The factors that influence the success rate of using ECMO in patients are age, gender, comorbidities, and complications during the initiation process. Conclusion: Different reports showed that COVID-19 patients with ARDS have a high mortality rate. Therefore, alternative therapy such as ECMO should be provided to prolong life expectancy by considering the patient's indications and contraindications before the initiation of the process.

Keywords: COVID-19, *Extracorporeal Membrane Oxygenation*/ECMO, and *Acute Respiratory Distress Syndrome*/ARDS.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It progresses to severe pneumonia characterized by bilateral interstitial infiltrates. Furthermore, it may develop into acute respiratory distress (ARDS) and failure due to ventilation/perfusion imbalance [1], The majority of patients are placed under respiratory assistance in the intensive care unit (ICU) [2].

COVID-19 continues to spread exponentially in most countries, placing an unprecedented burden on the healthcare and economy sectors. On September 6, 2020, the cumulative confirmed cases were 27,083,427. On a global scale, a total of 884,029 deaths were reported in 203 countries and territories (WHO, 2019). The number of cases is increasing rapidly with most falling in critical condition. Mortality and morbidity rates in COVID-19 patients with critical conditions are still quite high. This study showed that most of the critically infected patients had organ dysfunction, where 67%, 29%, 29%, 23%, and 2% had Acute Respiratory Distress Syndrome (ARDS), liver dysfunction, Acute Kidney Injury (AKI), cardiac injury, and pneumothorax respectively [4].

SARS-CoV-2 infections mostly develop into acute respiratory distress syndrome (ARDS). The prevalence of ARDS caused by COVID-19 is around 8.2%, and it requires mechanical ventilation and prone position [5]. However, this group of patients suffers from persistent hypoxemia and ARDS, which is difficult to treat despite the maximum conventional treatment with mechanical ventilation. In addition, the mortality among this subgroup is very high. Preliminary reports from China, Italy, and the United States showed high patient admissions to intensive care units (ICU) and mechanical ventilation with increased mortality rates due to COVID-19 [2].

In many cases of ARDS, respiratory failure occurs and is resistant to mechanical ventilation and other medical therapies. Therefore, Extracorporeal Membrane Oxygenation (ECMO) is considered as an alternative therapy [6]. The two basic methods used in ECMO therapy are Vena to Venous ECMO (VV-ECMO) and Vena to Artery ECMO (VA-ECMO). Regarding respiratory failure in COVID-19 patients, VV-ECMO is recommended as a therapeutic method. It allows ultra-protective ventilation by decreasing tidal volume and respiratory rate as well as increasing patient oxygenation as evidenced by an increase and decrease in the PaO_2/FiO_2 ratio and oxygenation index respectively [7]. Previously, a study conducted on Middle East Respiratory Syndrome (MERS) patients with refractory ARDS, showed that ECMO is successfully used as rescue therapy. This is because it is associated with lower mortality when compared to the conventional mechanical ventilation group [8].

ECMO therapy is used to treat COVID-19 cases with ARDS refractory to mechanical ventilation, muscle relaxation, and supine position or cardiogenic shock refractory to inotropic and vasopressor support. This should be conducted according to the guidelines recently published by the Extracorporeal Life Support Organization (ELSO). Therefore, this study aims to identify the effectiveness of Extracorporeal Membrane Oxygenation

(ECMO) therapy in prolonging the life expectancy of COVID-19 patients with ARDS in the intensive care unit (ICU). This is conducted with the consideration of the current pandemic and the fact that there is little experience using ECMO to assist patients.

2. METHOD

This literature review aims to identify and summarize previously published articles, avoid duplication of research, and obtain new themes that have not been examined[9]. Furthermore, article search, data extraction, analysis, and interpretation of the results were carried out using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyzes) guidelines. The literature review was conducted by searching for articles through accredited journal sites such as Elsevier, Science Direct, Springer, and PubMed. Additionally, the search was conducted using the keywords COVID-19, Extracorporeal Membrane Oxygenation/ECMO, and Acute Respiratory Distress Syndrome/ARDS. After collecting the literature, the selection was made by filtering according to specified inclusion and exclusion criteria.

The inclusion criteria established during the selection of items included the following: 1) Adult COVID-19 patients diagnosed with ARDS in the ICU, 2) COVID-19 patients with ARDS receiving ECMO therapy, 3) Mortality of COVID-19 patients with ARDS, 4) Articles written in Indonesian and English, and 5) Articles in the form of full text (full text). Meanwhile, the specified exclusion criteria were: 1) Publication articles in the form of case reports, meta-analyses, or literature reviews and 2) Published articles without available data.

The search was performed based on keywords and found 157 published articles were obtained. However, about 30 were removed leaving only 127 due to duplication. After reviewing the titles and abstracts, 32 matched articles were obtained while 95 were excluded because they did not meet the eligibility criteria. Furthermore, a full-text review was conducted on 32 articles that had previously been reviewed, and 26 were excluded because they did not use ECMO therapy as the main intervention (n = 20), where (n = 3) used qualitative method and Spanish. After the data extraction process, a total of 6 articles were included in this study.

Figure 1. PRISMA flow chart for article selection

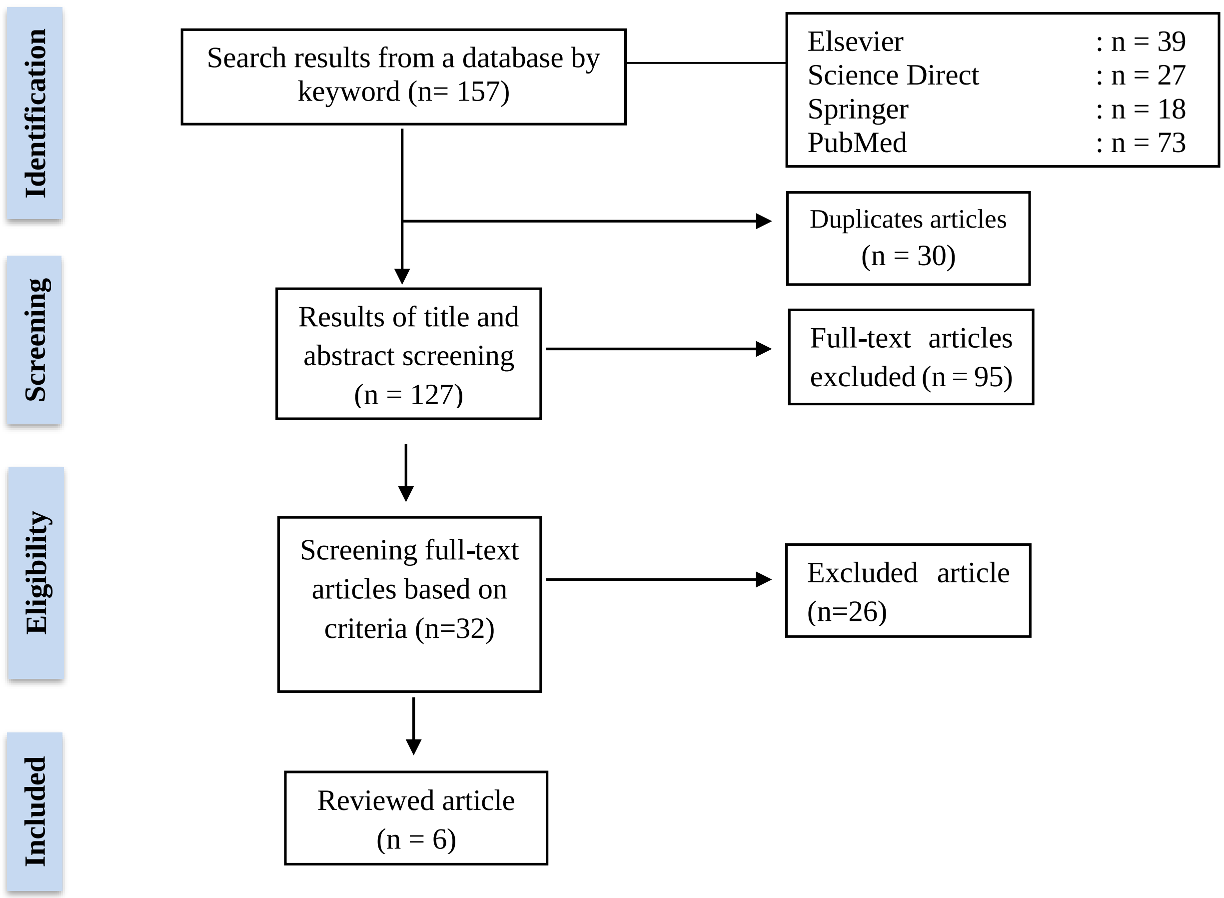

Table 1. Characterization of articles included in the research (n=6)

No.	Title, Author	Objective	Sample	Analysis Method	Results
1.	Mortality Risk Assessment in COVID-19 Venovenous Extracorporeal Membrane Oxygenation Tabatabai *et al*, 2021	Identify the survival of patients with COVID-19 undergoing VV-ECMO cannulation	40 COVID-19 patients with ARDS cannulate using VV-ECMO	Univariate and bivariate analysis	A total of 40 COVID-19 patients with ARDS were cannulated using VV-ECMO. A total of 33 patients (82.5%) completed ECMO therapy, 18 (54.5%) were decannulated from ECMO and 18 were discharged from the hospital, while 15 patients (45.5%) died. A total of 7 patients (17.5%) remained on ECMO at the time of analysis. Of the 18 that survived until discharge from the hospital, 14 (77.8%) went home, and 4 patients (22.2%) were discharged to a rehabilitation facility.
2.	Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019: Crisis Standards of Care Agerstrand *et al.*, 2019	Evaluate survival outcomes in ECMO-assisted COVID-19 patients and describe programmed adaptations made in response to pandemic-related crisis conditions	22 patients with COVID-19	Descriptive statistics	The study was conducted on 22 patients with COVID-19 placed on ECMO during the research period. The mean age was 52 years and 18 (81.8%) were male. A total of 21 patients (95.4%) had severe ARDS and 7 (31.8%) had heart failure. About 15 patients (68.1%) were managed with venovenous ECMO while 7 (31.8%) required arterial assistance. A total of 12 (54.5%) were transported by ECMO from an external institution. A total of 12 patients were discharged alive from the hospital (54.5%).

					Extracorporeal membrane oxygenation had been used successfully in patients with respiratory and cardiac failure due to COVID-19. The process was continued using ECMO, including ECMO transportation, during crisis conditions is possible even at the height of the COVID-19 pandemic.
3.	Extracorporeal Membrane Oxygenation for SARS-CoV-2 Acute Respiratory Distress Syndrome: A Retrospective Study From Hubei, China Yang *et al.*, 2021	Identify the long-term effects of using ECMO therapy in COVID-19 patients with ARDS	73 patients with COVID -19	Kaplan Meier	The study was conducted on 73 patients treated with ECMO with a mean age of 62 (range 33-78) years and 42 (63.6%) were male. Before initiation of ECMO, the patient had a severe respiratory failure on mechanical ventilation with PO. FiO_2 of 71.9 mmHg and PCO of 62 mmHg were found on arterial blood analysis. The mean duration from symptom onset to invasive mechanical ventilation and ECMO initiation was 19 days to 23 days. Before and after ECMO initiation, the proportion of patients receiving prone ventilation was 58.9 and 69.9%, respectively. The average duration of ECMO assistance was 18.5 days. During treatment with ECMO, major bleeding occurred in 31 (42.5%) patients, and the oxygenator was changed in 21 (28.8%) patients. Since the start of ECMO, the 30-day and 60-

					day mortality were 63.0 and 80.8%, respectively.
4.	SARS-CoV-2 and ECMO: early results and experience Akhtar *et al*, 2021	Identify the mortality rate of COVID-19 patients with ARDS using ECMO therapy	18 COVID-19 patients managed with extracorporeal assistance	Descriptive statistics	The study was conducted on 18 patients managed with extracorporeal assistance and found that 14 of patients survived (78%) with 4 deaths (22%). Furthermore, the survival rate in this group was 14 (78%). Of the 4 deaths, 2 were caused by bleeding.
5.	Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study Schmidt *et al.*, 2020	Identify patients' characteristics and outcomes with respiratory failure and COVID-19 treated with ECMO.	83 COVID-19 patients	Descriptive statistics	The study was conducted on 492 COVID-19 patients. It was found that 83 patients received ECMO assistance, male, and have a mean age of 49 years. Pre-ECMO procedures performed included: prone position, continuous neuromuscular blockers, and nitrate oxidation. Meanwhile, ECMO assistance was successful in reducing tidal volume, respiratory rate, and plateau pressure for 24 hours after initiation. At ECMO, 67 (81%) patients were in the prone position, 80 (96%) received continuous neuromuscular blockers, 5 (6%) nitric oxide, and 17 (20%) high-dose corticosteroids (Table 3). The mean activated partial thromboplastin time ratio increased progressively over days 1-3 at ECMO. The mean duration of ECMO assistance was 20 days and ICU stay was 36 days.

6.	Extracorporeal Membrane Oxygenation Support in Severe COVID-19 Kon *et al.*, 2021	Describe the implementation and management of ECMO assistance for patients with COVID-19 and report promising results.	27 patients receiving ECMO supportive therapy	Descriptive statistics	The results showed that 321 patients were intubated for COVID-19, 77 patients (24%) were evaluated for ECMO assistance, and 27 patients (8.4%) were placed on ECMO. All patients were assisted with venovenous ECMO. Furthermore, the current survival was 96.3%, with only 1 death to date in over 350 days of total ECMO support. A total of 13 patients (48.1%) remained on ECMO support, and 13 patients (48.1%) were successfully decannulated. As many as 7 patients (25.9%) were discharged from the hospital, 6 (22.2%) remained in the hospital, 4 underwent active cardiopulmonary resuscitation.

3. RESULTS

The results showed that 6 reviewed studies were conducted at different institutions. In the United States, 3 studies were conducted namely [10], [11], [15]. Meanwhile, the remaining were conducted in Hubei, China [12], London, UK [13], and Paris, France [14] using a retrospective design. The survival of COVID-19 patients with ARDS that were given ECMO supportive therapy was identified through 6 studies presented in the table above. Furthermore, the effectiveness of using ECMO therapy in prolonging the life expectancy of patients with ARDS was quite high as shown in 6 different studies presented above. In a conducted by Tabatabai et al. (2021) 40 COVID-19 patients with ARDS were cannulated using VV-ECMO. A total of 18 patients (45%) survived and were discharged from the hospital, while 15 (37.5%) died and 7 (17.5%) remained on ECMO at the time of analysis[10].

Agerstrand et al., 2021 reported high survival rates in COVID-19 patients with ARDS that received ECMO-supported therapy. The study showed that 21 patients (95.4%) had severe ARDS and 7 (31.8%) had heart failure. A total of 15 patients (68.1%) were managed with venovenous ECMO while 7 (31.8%) required arterial support. Meanwhile, 12 patients (54.5%) were declared safe and discharged from the hospital and 10 (45.5%) died[11]. Similarly, the study conducted by Kon et al., (2021) showed a survival rate of 96.3% with only 1 death out of the 27 patients that were given ECMO therapy. A total of 13 patients (48.1%) remained on ECMO assistance, while 13 (48.1%) were successfully decannulated. A total of 7 patients (25.9%) were discharged from the hospital, 6 (22.2%) were still receiving treatment at and 4 of them were undergoing active cardiopulmonary resuscitation[15]. The same results were also obtained by Schmidt et al., (2020), in which 83 patients that received ECMO support were male and the mean age was 49 years. A total of 48 patients (58%) survived and were decannulated from ECMO, 5 (6%) were still receiving ECMO therapy in the ICU, while 30 (36%) died[14]. A study conducted by Akhtar et al., 2021 also reported a relatively high life expectancy in COVID-19 patients with ARDS that received ECMO therapy. The results showed that of 18 patients treated with ECMO, 14 survived (78%) and 4 died (22%). Of the 4 deaths, 2 were due to intracranial hemorrhage and 2 had discontinued life support therapy due to progressive multi-organ failure[13]. Conversely, the study conducted by Yang et al. (2021) showed different results, and it showed a high mortality rate in patients with ARDS receiving ECMO therapy. The death occurred in 59 patients (81%) and about 14 (19%) survived after undergoing ECMO therapy[12].

4. DISCUSSION

COVID-19 causes acute respiratory failure that requires intensive care unit (ICU) and mechanical ventilation support. However, the most serious conditions can rapidly progress to acute respiratory distress syndrome (ARDS) with severe hypoxemia and death. These can occur despite the conduction of mechanical ventilation of the lungs. Simply, ARDS can be treated by lowering the tidal volume and administering Positive End-Expiratory Pressure (PEEP) at a higher pressure. In contrast, COVID-19 patients with ARDS face a highly abnormal coagulation cascade, leading to pulmonary coagulopathy and high ventilation-perfusion mismatch [10]. Furthermore, most studies showed that SARS-CoV-2 directly attacks alveolar epithelial cells which can cause pulmonary edema, hyaline membrane formation, and lung lobe collapse [16]. Endothelial injury can also lead to hypoxic pulmonary vasoconstriction failure. These can affect pulmonary vascular function and cause a ventilation-perfusion mismatch. Moreover, pulmonary vascular thrombosis and/or pulmonary embolism may exacerbate hypoxemia. High levels of secreted cytokines secondary to neutrophil activation may also contribute to the development of ARDS in patients [17].

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) indicate the possibility of treatment by ECMO in critical conditions. The treatment with ARDS requires multidisciplinary expertise, especially during pandemic conditions where there is a surge in patient numbers [18]. Furthermore, they have a high risk of death, therefore, ECMO is a supportive modality for patients who fail conventional management and may improve survival [19]. ECMO is an Extracorporeal Life Support (ECLS) used to oxidize blood to temporarily compensate for a failed lung or heart by minimizing further iatrogenic ventilator-induced lung injury [20]. Furthermore, it provides full or partial extracorporeal lung assistance by adjusting blood flow (which can be up to 7 L/min). Oxygen flow assistance by ECMO is required with respiratory distress, and in obese patients, it can reach 5 L/min to meet systemic oxygen requirements [21].

Another study was conducted on the collection of baseline mortality and morbidity data on the use of ECMO for ARDS patients caused by SARS-CoV-2. It showed a high mortality rate for patients aged 60 years treated with ECMO in Hubei, China, for a relatively long period [12]. The higher mortality associated with patients receiving ECMO or conventional mechanical ventilation for ARDS is attributed to cytokine production. Furthermore, there is accumulating evidence to suggest that a subgroup of patients with severe COVID-19 disease have a cytokine storm syndrome. It is an activated cascade that causes harmful automatic amplification of inflammatory cytokine production leading to end-organ damage and a higher risk of death. There is a strong positive correlation between mortality and high levels of cytokines, particularly Interleukin-6 for patients that have received ECMO [22]. Ruan et al, found that Interleukin-6 concentrations differed significantly between non-survivors and survivors, and those that did not survive had values up to 1.7 times higher[23].

Early treatment should commence for those that received ECMO therapy without clear contraindications. This should be conducted with a complete understanding of the ECMO mode and the different oxygen distributions. Besides, a full assessment of the patient's cardiac and respiratory function should be performed. The appropriate mode should also be selected to improve patient survival. Several other factors such as gender, age, comorbidities, and clinical manifestations can influence the success of ECMO therapy [24]. This causes shortages of ECMO devices in some health care centers. Therefore, it is imperative to prioritize patients that are most eligible for ECMO therapy. It should be used specifically for certain patient groups because they have a higher survival rate and support the effectiveness of ECMO use.

The limitations of the study during the review process are the use of retrospective design, information regarding the setting of ECMO, data on demographic information, complications, the timing of critical events, and incomplete patient survival status. Furthermore, there was no comparison between the different respiratory support strategies in patients with ARDS due to a lack of literature.

5. CONCLUSION

It is reasonable to conclude that the administration of ECMO therapy is quite effective in prolonging the life expectancy of COVID-19 patients with ARDS. This was conducted by prioritizing patients aged <60 years, with relatively low comorbidities or without serious complications during the initiation of ECMO, and with a high acceptable probability for correcting typical pulmonary failure.

AUTHORS CONTRIBUTIONS

All authors conceived concept and design, data collection, data analysis and interpretation, manuscript draft.

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