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Extracorporeal membrane oxygenation (ECMO) in patients with COVID-19: a rapid systematic review of case studies

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Abstract. – OBJECTIVE: COVID-19 can cause severe acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation (ECMO) can support gas exchange in patients failing conventional mechanical ventilation, but its role is still controversial. We performed a rapid systematic review focusing on the use of ECMO in patients with COVID-19.

MATERIALS AND METHODS: PubMed/MEDLINE, Google Scholar, Embase, the Cochrane Library, EBSCO and Ovid (updated 30 April 2020) were systematically searched. Case reports/Case series from COVID-19 patients treated with ECMO were included in the study. Three reviewers assessed, selected, and abstracted data from studies. All disparate opinions were resolved through discussion.

RESULTS: We included 13 articles for systematic evaluation, including 10 case reports and 3 case series studies, with a total of 72 patients. We search for the following information: First author of articles; Patient's location; age; gender; body mass index (BMI); Comorbidities; Time on ECMO; Mode of ECMO; treatments and clinical outcomes. As of all reporting times, our data show that 38 patients (52.8%) have died definitively, 13 patients (18.0%) were still receiving ECMO treatment, 12 patients (16.7%) were alive, 7 patients (9.7%) were recovery and 2 cases (2.8%) remained hospitalized.

CONCLUSIONS: ECMO plays an important role in the stabilization and survival critically ill patients with COVID-19, but the usefulness of ECMO in reducing the mortality of severe ARDS caused by COVID-19 was limited. Therefore, a larger sample size study and a comprehensive analysis of evaluating the medical value of using ECMO on COVID-19 patients are urgently required.

Key Words:

Extracorporeal membrane oxygenation, COVID-19, Hypoxemia, Acute respiratory distress syndrome, Systematic review.

Abbreviations

COVID-19: Coronavirus disease detected in 2019; ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; BMI: body mass index; WHO: The World Health Organization; ELSO: The Extracorporeal Life Support Organization; ASAIO: The American Society for Artificial Internal Organs; ICU: intensive care unit; H1N1: The influenza A; ALI: acute lung injury; MERS: The Middle East respiratory syndrome.

Introduction

Since early December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has occurred in Wuhan, China[1-5]. The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak to be a pandemic on March 12, 2020[6]. The novel coronavirus SARS-CoV-2 is infecting hundreds of thousands of humans around the globe since the end of 2019[7,8]. In severe cases of COVID-19, patients can rapidly progress to acute respiratory distress syndrome (ARDS) and most of these deaths were due to severe respiratory failure[1-3,9]. In an earlier single-center, retrospective, observational study, Yang et al[10] reported on 52 critically ill patients with characterised by severe hypoxaemia at Wuhan Jin Yin-tan hospital (Wuhan, China), which is a designated hospital to treat patients with SARS-CoV-2 pneumonia. The 28-day mortality of critically ill COVID-19 patients is 62.5%. Of all included patients, 71% required mechanical ventilation and 67% had ARDS[10].

Extracorporeal membrane oxygenation (ECMO) is an advanced form of life support for

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critically ill patients, which can provide effective respiratory and cardiac support[11,12]. According to the interim guidance formulated by WHO[13], ECMO should be considered as a rescue therapy for COVID-19 patients with ARDS. ECMO can be a life-saving therapy for critically ill patients with refractory hypoxemia. Recently, The Extracorporeal Life Support Organization (ELSO)[14] and The American Society for Artificial Internal Organs (ASAIO)[15] both published guidelines about the role of ECMO in treating patients with COVID-19. To date, the role and outcome of ECMO in the management of COVID-19 is currently unclear[16]. There is little experience with using ECMO to support COVID-19 patients. With the increase of COVID-19 critical patients with refractory hypoxemia, it is urgent to enhance our understanding of the role of ECMO in the treatment of severely ill patients with COVID-19. According to early experience from an intensive care unit (ICU), ECMO can support gas exchange in patients failing conventional mechanical ventilation, but its role is still controversial[17-19]. Thus, we performed a rapid systematic review focusing on the use of ECMO in patients with COVID-19.

Materials and Methods

Search Strategy

PubMed/MEDLINE was searched for articles on ECMO in patients with COVID-19 infection with the following highly sensitive strategy: (coronavirus OR COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR pandemic OR epidemic) AND (ards OR (acute AND respiratory AND distress AND syndrome) OR ali OR (acute AND lung AND injury) OR arf (acute AND respiratory AND failure) OR (pulmonary AND failure) OR (pulmonary AND insufficiency) OR (respiratory AND failure) OR (respiratory AND insufficiency)) AND (ecmo OR (extracorporeal AND membrane AND oxygenation)). In addition, Google Scholar, Embase, the Cochrane Library, EBSCO and Ovid were also systematically queried. All searches were updated on 30 April 2020. Limits were set to literatures published in English. Moreover, relevant references were manually searched by trained researchers for additional studies.

Inclusion and Exclusion Criteria

Case reports/Case series from COVID-19 patients treated with ECMO were included in the study and all patients with laboratory-confirmed COVID-19 infection. We analyzed with descriptive statistics. Of these, we excluded non-English-language articles, as well as those for which no full text was available.

Data Extraction and Management

Two reviewers (HBS and JLX) independently screened the titles and abstracts identified by the search. For preliminarily eligible studies, two reviewers (HBS and JLX) read the full text and enrolled the studies. The data were extracted by another two reviewers (HBS and HMZ). One reviewer entered the data into the table, and the second reviewer checked the entries for accuracy. All disparate opinions were resolved through discussion.

Assessment of the Quality of the Studies

Evidence synthesis was descriptive, because data were not suitable for meta-analysis. We did not attempt to rate the quality of included studies in this rReview. Instead, we considered potentially important limitations qualitatively for each study.

Results

Study Selection

The search identified 258 records; manual reference searching identified an additional 16 records. 138 study abstracts were screened after removing duplicates and 98 selected for full text analysis. After full text reading, 85 articles did not meet inclusion criteria and 13 articles were included in the review[20-32]. We search for the following information: First author of articles; Patient's location; Age; Gender; Body mass index (BMI); Comorbidities; Time on ECMO; Mode of ECMO; Treatments and clinical outcomes. In conclusion, we formed a search flow diagram according to the data evaluation (Figure 1).

Patients and Characteristics

We included 13 articles for systematic evaluation, including 10 case reports[20-29] and 3 case series studies[30-32], with a total of 72 patients. Of the 72 cases with COVID-19 treated with ECMO, two have been reported in Germany and France, and one each in Japan, Switzerland and Italy. China, the country where the outbreak first occurred, has reported 22 cases. The United States, by far the most confirmed country, has reported 43 cases. Most of the 72 patients were male (53

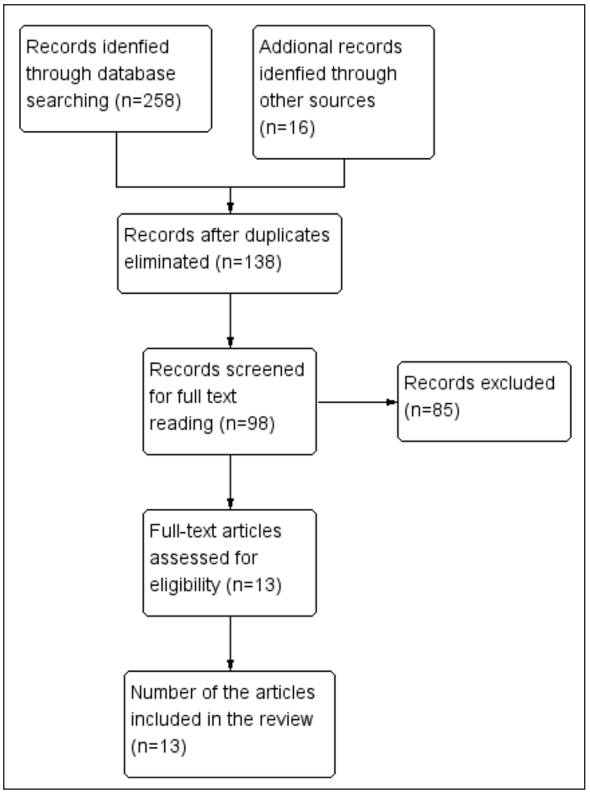

Figure 1. Flow chart of the study.

cases). In these cases, the majority of patients were middle-aged and elderly. In the available data, the median BMI was 33 kg/m^2 in a case series of 10 cases and 8 patients had a BMI over 24 kg/m^2 in 10 case reports. Most of the people had comorbidities including hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, obstructive sleep apnea, asthma and obesity. During the data about all 32 patients[31],14 patients (43.8%) had obesity, 11 patients (34.4%) had diabetes, 4 patients (12.5%) had heart disease, 3 patients (9.4%) had cancer, and 3 patients (9.4%) had asthma. This case series reported 10 patients who were placed on ECMO for COVID-19 in the state of Pennsylvania and 7 of 10 patients (70%) had comorbid conditions[32] (Table I).

Managements, Treatments and ECMO Outcomes

According to the data, the time to treat COVID-19 with ECMO is uncertain. Of the available data, 40 patients received veno-venous ECMO and 7 patients with cardiopulmonary dysfunction received veno-arterial ECMO. In terms of treatment, most patients receive mechanical ventilation, antibiotic treatment, antiviral therapy and supportive therapy based on symptoms. Some patients were injected with steroids. Regarding the use of hydroxychloroquine, only one case (3.1%) in a series of 32 patients was reported to have received hydroxychloroquine[31]. In a series of 10 cases, all patients (100%) were treated with hydroxychloroquine[32]. As of all reporting times, our data show that 38 patients (52.8%) have died definitively, 13 patients (18.0%) were still receiving ECMO treatment, 12 patients (16.7%) were alive,7 patients (9.7%) were recovery and 2 cases (2.8%) remained hospitalized (Table II).

Discussion

ECMO is one of the methods of extracorporeal circulation and ventilation support, primarily adopted to partially or completely replace the cardiopulmonary function of patients to protect the oxygen supply of the organs and strive for time to treat primary diseases[33,34]. The COVID-19 pandemic is causing an increasing number of critically ill patients worldwide. This comprehensive systematic review based on 10 case reports and 3 case series studies, pooling data on the outlook of ECMO in 72 patients with confirmed COVID-19. Our preliminary analysis shows that treatment of ECMO is reasonable and valuable in COVID-19 patients with comorbidities. However, the usefulness of ECMO as a rescue therapy in reducing the mortality of severe ARDS caused by COVID-19 is limited so far.

According to the experience with the use of ECMO in previous outbreaks of viral respiratory syndromes[35,36], ECMO may play a role in the treatment of ARDS patients and in reducing their mortality. The influenza A (H1N1) pandemic caused thousands of deaths worldwide in 2009. ECMO has benefitted patients with severe respiratory failure who likely would have died without it[37,38]. In a meta-analysis including 8 studies and 266 patients, the results of this study indicate that ECMO is feasible and effective in patients with acute lung injury (ALI) due to H1N1 infection[39]. The Middle East respiratory syndrome (MERS), caused by a coronavirus (MERS-CoV), is an infectious disease. In a retrospective analysis on 35 MERS-CoV patients in ICUs with refractory respiratory failure, those who were treated with ECMO had significantly lower in-hospital mortality (65 *vs.* 100%; $p = 0.02$), compared with those who received conventional therapy[36]. There is little worldwide experience with using ECMO

Table I. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

First author	Published (n)	Location	Age (years)	Sex	BMI (kg/m^2)	Comorbidities
Bemtgen et al[20]	Case report (n=1)	Germany	52	M	25.5	Dilated cardiomyopathy
Nakamura et al[21]	Case report (n=1)	Japan	45	M	NA	Diabetes; Hypertension; Asthma
Hartman et al[22]	Case report (n=1)	Swedish	44	M	NA	Hypertension; Hyperlipidemia
Tavazzi et al[23]	Case report (n=1)	Italy	69	NA	NA	NA
Shen et al24	case report (n=1)	China	60s	M	NA	Hypertension; Mitral insufficiency
Yousefzai et al[25]	Case report (n=1)	USA	56	M	NA	Hypertension
Zhan et al[26]	Case report (n=1)	China	54	M	NA	NA
Koehler et al[27]	Case report (n=1)	Germany	62	F	31.5	Hypertension; Obesity; Hypercholesterolemia; COPD
Abou-Arab[28]	Case report (n=2)	France	59	F	41	Morbid obesity
			67	M	34	Obesity
Li et al[29]	Case report (n=8)	China	64	M	24.5	Hypertension
			81	M	23.8	Hypertension; Cardiovascular disease
			62	M	24.3	None
			75	M	22.4	Bladder cancer
			65	M	20.8	Hypertension; Diabetes; CI; MN
			63	F	24.2	None
			25	M	40.8	None
			79	F	23.6	Hypertension; CI
Zeng et al[30]	Case series (n=12)	China	Mean (50.9)	M (n=11); F (n=1)	NA	Hypertension (n=1); Diabetes (n=1); Heart disease (n=1); Hyperthyroidism (n=1)
Jacobs et al[31]	Case series (n=32)	USA	Mean (52.4)	M (n=22); F (n=10)	NA	Cancer (n=3); Diabetes(n=11); Heart Disease(n=4); Obesity(n=14); Asthma(n=3)
Sultan et al[32]	Case series (n=10)	USA	Range from 31 to 62	M (n=7); F (n=3)	Median (33)	Seven (70%) patients: hypertension, diabetes, hyperlipidemia, asthma, obstructive sleep apnea, SLE, G6PD

BMI, body mass index; M, male; F, female; NA, not available; COPD, chronic obstructive pulmonary disease; CI, cerebral infarction; MN, membranous nephropathy; SLE, systemic lupus erythematosus; G6PD, glucose-6-phosphate-dehydrogenase deficiency.

to support COVID-19 patients, although we have some relevant experience in the treatment of influenza and viruses.

The primary manifestation of COVID-19 is respiratory symptoms, some patients had severe cardiovascular damage[9]. Patients with cardiovascular disease had an increased risk of death[40,41]. ECMO was a feasible salvage modality in COVID-19 patient with cardiopulmonary dysfunction. Veno-veno ECMO can be used to support isolated respiratory failure, and veno-arterial ECMO might be used if the patients had cardiac diseases[42]. However, the role of ECMO in the management of COVID-19 is unpromising in early reports. To date, there is not enough evidence to support its use in mainland China. Three studies pooled the results of ECMO therapy in COVID - 19 patients in mainland China and evaluated ECMO mortality as reported in early COVID-19 epidemiological studies[17-19]. Henry et al[19] found that mortality in ECMO versus conventional therapy was not significantly different (OR: 2.00, 95% CI: 0.49-8.16). According to early ECMO treatment of COVID - 19 patients in mainland China, the use of ECMO seems to have substantially higher mortality. In particular, older patients with multiple comorbidities had a higher mortality rate. Among COVID-19 patients which have received ECMO, a strong positive correlation exists between mortality and high cytokine

Table II. Management, treatments and ECMO outcomes for critically ill COVID-19 patients.

First author	Number of patients (n)	Time of ECMO (days)	Mode of ECMO	Treatments	Prognosis
Bemtgen et al[20]	n=1	20	V-A	1, 2, 3, 5	On ECMO
Nakamura et al[21]	n=1	11	V-V	1, 2, 3, 5	Recovery
Hartman et al[22]	n=1	7	V-V	1, 2, 3,5	Recovery
Tavazzi et al[23]	n=1	12	V-A	1,5	Recovery
Shen et al[24]	n=1	5	NA	1, 3, 4, 5	Remained hospitalized
Yousefzai et al[25]	n=1	NA	V-A	5	Remained hospitalized
Zhan et al[26]	n=1	5	V-V	1, 2, 3, 4, 5	Recovery
Koehler et al[27]	n=1	NA	V-V	1, 5	Died
Abou-Arab et al[28]	n=2	NA	NA	1, 3, 5	On ECMO
		NA	V-V	1, 5	On ECMO
Li et al[29]	n=8	40	V-V	NA	Recovery
		47	V-V	NA	Died
		47	V-V	NA	Recovery
		37	V-V	NA	Died
		22	V-V	NA	Recovery
		33	V-V	NA	On ECMO
		10	V-V	NA	Died
		3 hours	ECPR-VA	NA	Died
Zeng et al[30]	n=12	Mean (11.3)	NA	1 (100%); 2 (100%); 3 (100%); 4 (83.3%); 5 (100%)	Died (n=5); Alive (n=7)
Jacobs et al[31]	n=32	Mean (7.33)	Unknown (n=1); VA (n=3); V-AV to V-V (n=1); V-V (n=25); V-V, VV-A (n=1); V-V, VV-V (n=1)	1 (100%); 3 (18.8%); 4 (15.6%); 5 (100%); 6 (3.1%)	Died (n=27); Alive (n=5)
Sultan et al[32]	n=10	Median Time (11)	NA	1 (100%); 2 (70%); 3 (40%); 4 (40%); 5 (100%) 6 (100%)	Died (n=1); On ECMO (n=9)

ECMO, extracorporeal membrane oxygenation; NA, not available; V-A,veno-arterial ECMO; V-V,veno-venous ECMO; ECPR-VA, extracorporeal cardiopulmonary resuscitation-veno-arterial; V-AV, ECMO with systemic venous inflow with dual systemic venous and systemic arterial outflow (i.e., V-V and V-A combined); VV-A,V-A ECMO with dual systemic venous cannulation for inflow (typically bicaval systemic venous drainage); VV-V,V-V ECMO with dual systemic venous cannulation for inflow (typically bicaval systemic venous drainage); 1: Mechanical ventilation; 2: Antibiotic treatment; 3: Antiviral therapy; 4: Intravenous Steroids; 5: Supportive therapy based on symptoms; 6: Hydroxychloroquine.

levels, most notably IL-6[43-45]. We hope that these studies of cytokine analysis may explain the high mortality of patients treated with ECMO.

In fact, many factors may influence the outcome of ECMO treatment, including mechanical ventilation duration, the severity of underlying disease, the experience of trained medical staff, and ECMO equipment[17]. ECMO is a limited medical resource that requires a well-trained team, especially in highly affected areas with limited resources and personnel[46]. Many countries affected COVID-19 may not be able to afford this expensive technology. ECMO is not the only factor to improve the condition of COVID-19 patient, the combined effect of anti-shock therapy, hormone and antiviral therapy and it helps patient to survive. During the treatment of ECMO, coagulation function and blood gas were monitored and chest radiographs were taken periodically to prevent complications during treatment[26]. Echocardiography is a useful tool in the management of respiratory and hemodynamic monitoring and guidance in the treatment of patients with COVID-19 pneumonia and is particularly beneficial to critically ill patients[47].

COVID-19 is a novel coronavirus disease in which the causative pathogen is highly contagious and is transmitted typically via respiratory droplets/fomites[48,49]. In addition to the sterile gowns, gloves, and hats used in the operating room, all related staff must wear appropriate personal protective equipment[50], including appropriate N-95 masks and full protective eye-wear when manipulating ECMO[51]. Some approaches, such as intubation and sputum suction, pose a high risk of infection for medical staff[17]. Therefore, all medical staff should be supplied with sufficient protection when contacting COVID-19 patients.

There are some limitations in the present review. (1) We did not include non-English publications in the review. (2) This study conducted a systematic analysis based on 10 case reports and 3 case series. We didn't have enough data for a meta-analysis. (3) We cannot exclude the risk of publication bias. (4) This systematic review is also not powerful enough to define the exact role of different types of ECMO. (5) Detailed data on patient outcomes are incomplete. In addition, more collaborative research efforts are clearly needed.

Conclusions

In summary, ECMO plays an important role in the stabilization and survival of critically ill patients with COVID-19. Based on the analysis of 72 cases and review of the literature, the usefulness of ECMO in reducing the mortality of severe ARDS caused by COVID 19 was limited. Therefore, a larger sample size study and a comprehensive analysis of evaluating the medical value of using ECMO on COVID-19 patients are urgently required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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