SYSTEMATIC REVIEW

Role of Invasive Mechanical Ventilation and ECMO in the Management of COVID-19: A Systematic Review

Sanjana Nagraj[1], Rutu Karia[2], Sahar Hassanain[3], Prithwish Ghosh[4], Viraj R Shah[5], Abin Thomas[6]

Abstract

Objectives: This systematic review aims to provide insight into the outcome of extracorporeal membrane oxygenation (ECMO) and invasive mechanical ventilation use in critically ill COVID-19 patients.

Data sources: Electronic databases PubMed Central and PubMed were searched from January 2020 to June 2020 for published studies about ECMO and/or invasive mechanical ventilation use in COVID-19 patients. Data Extraction and Study Selection: The search strategy retrieved 766 articles, of which 19 studies consisting of 204 patients fulfilled the inclusion criteria and were included in the analysis.

Data synthesis: Primary outcomes evaluated were discharge and/or clinical improvement and mortality rate. Secondary outcomes evaluated included reported complications and the mean number of days of hospitalization for survivors. Weighted averages of included studies were calculated, and data were pooled in forest plots. Nearly, 68.1% of the patients received invasive mechanical ventilation without ECMO support, and 31.9% were placed on ECMO. Also, 22.5% of the patients were discharged and/or clinically improved and 51.5% died. Twenty-six percent of the study population deteriorated but remained alive or experienced no improvement in clinical condition. And 75.2% of those who died belonged to the non-ECMO group and 24.8% to the ECMO group. The mortality rate in the non-ECMO group was 56.8% compared to 40% in the ECMO group.

Conclusion: The utility of ECMO during a pandemic is uncertain as it is a resource-intensive modality, especially when the mortality rate in severely ill patients infected with COVID-19 virus is already known to be high.

Keywords: Coronavirus disease 2019, COVID-19, Critically ill, Extracorporeal membrane oxygenation, Invasive mechanical ventilation, SARS-CoV-2 infection.

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Introduction

Development of respiratory failure resulting from worsening hypoxia and accompanying acute respiratory distress syndrome (ARDS) is pathognomonic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Reports from Wuhan, China, where the virus was first recognized, reported ARDS in 15 to 30% of their patients.[2-4] The World Health Organization (WHO) interim guidance for managing suspected COVID-19 recommends continuous oxygen support for mild to moderate ARDS ($PaO_2/FiO_2 \leq 200$ mm Hg at either a positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O, or in nonventilated patients), and consideration of mechanical ventilation for the severe form of ARDS ($PaO_2/FiO_2 \leq 100$ mm Hg despite providing a PEEP ≥ 5 cm H_2O, or in nonventilated patients). For refractory hypoxemia not amenable to lung-protective ventilation strategies, extracorporeal membrane oxygenation (ECMO) should be considered.[5]

Post hoc Bayesian analysis of data from the "ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial" reported posterior probability of mortality benefit of ECMO in severe ARDS.[6] However, expense, expertise, and complications, such as secondary infections, thrombosis, and hemorrhage, among others have limited its use in clinical practice.[1] With limited data available on ECMO use in the management of COVID-19, concrete guidelines on when to start ECMO support, the complications that can be expected, and whether it provides mortality benefit in SARS-CoV-2 infection are currently unknown.

We aimed to study the clinical profile, complications, and outcomes of COVID-19 patients who were intubated and mechanically ventilated and placed on ECMO.

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Conflict of interest: None

Data Retrieval

Materials and Methods

Electronic databases PubMed Central and PubMed were searched from January 2020 to June 2020 for published studies about ECMO and/or invasive mechanical ventilation use in COVID-19 patients. The combination of keywords used was "Extracorporeal membrane oxygenation" OR "ECMO" OR "invasive mechanical ventilation" OR "intubated and mechanically ventilated" AND "COVID-19." References from all eligible studies (including review articles) were reviewed for the possibility of finding additional studies.

Studies were eligible if they met the predefined inclusion criteria: (1) Proven SARS-CoV-2 infection by reverse transcription-polymerase chain reaction, (2) age >18 years, and (3) hospitalized patients on invasive mechanical ventilation or ECMO. Articles were excluded if (1) pregnant patients, (2) articles were not in English, or (3) review articles that reviewed original studies that were already screened through our search criteria, (4) studies published as abstracts only, or (6) did not meet the objective of our study. There was no restriction on the sample size. Since the current management of COVID-19 infection is multimodal, data from the subset of patients who were either placed on invasive mechanical ventilation or on ECMO support were selectively extracted, pooled, and analyzed. Two authors independently performed study selection as per the inclusion criteria and data extraction. The second review of all included studies was independently performed by the primary author to ensure conformity with the inclusion criteria and objectives of the study. Disagreements were resolved by discussion and general consensus. For all 19 studies, follow-up correspondence with the respective authors was done in order to get insight into the 28-day clinical status or end outcome of the included patients. Our search was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and is outlined in Flowchart 1.

Quality Assessment

Quality assessment of the included studies was conducted in compliance with the published criteria.[7,8] Quality of each of the included studies was evaluated by two coauthors independently. In the case of a disagreement, the primary author was approached, who then reviewed the study to reach a common consensus. Quality appraisal was done with the help of NIH Quality Assessment Tool for Case Series Studies whereby studies were rated as "good," "fair," or "poor" and NIH Quality Assessment Tool for Observational Cohort Studies.[8]

Data Pooling and Data Analysis

Extracted data were pooled and analyzed. Author, year of publication, study design, country of population, patient demographics, duration of hospitalization, indications for administering invasive mechanical ventilation and/or ECMO, duration of invasive mechanical ventilation, duration of ECMO, type and frequency of comorbidities, pharmacological and supportive management, type and frequency of complications, and outcomes of the included studies were recorded.

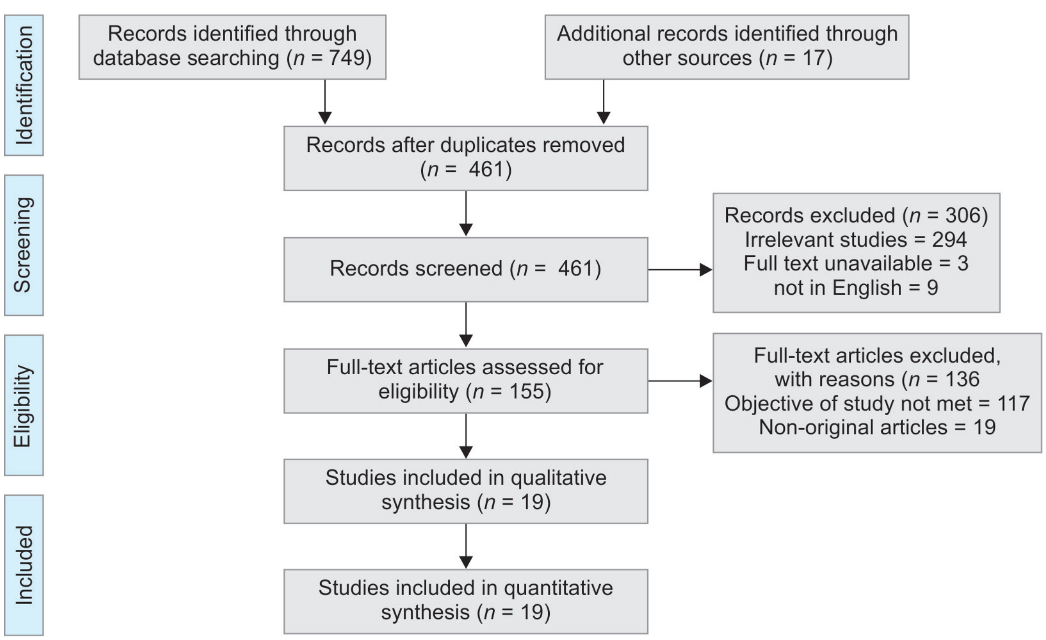
The primary outcomes analyzed in this study were discharge and/or clinical improvement and mortality rates. The secondary outcomes evaluated included the mean number of days of hospitalization for survivors and complications that arose in the study groups.

Results were reported as percentages, calculated from the total number of patients in the pooled analysis. Data were pooled and presented in the form of forest plots, tables, and graphs. Composite data from single-patient case reports have been labeled as "others" in forest plots in consideration of the sample size.

Review Results

Out of 766 articles, 19 studies met our predefined inclusion criteria and were included in the meta-analysis (Fig. 1). Characteristics of the included studies and baseline epidemiological features are described in Tables 1 and 2, respectively.

Flowchart 1: PRISMA Flowchart



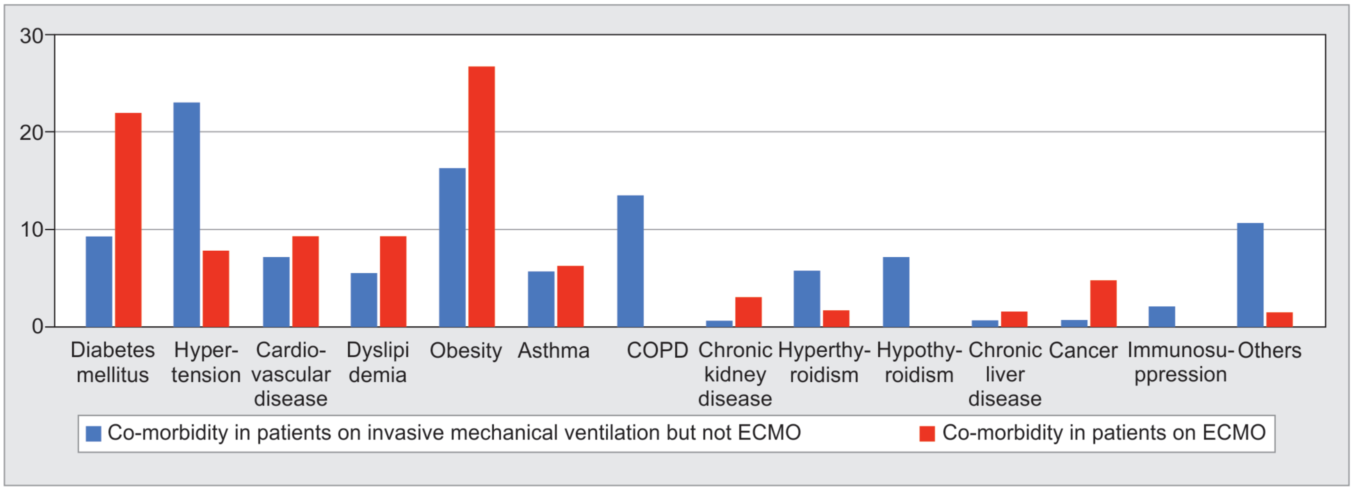


Fig. 1: Co-morbidity in patients on invasive mechanical ventilation but not on ECMO vs. patients on ECMO

Quality Assessment

Quality assessment of the included studies was conducted in compliance with the published criteria.[7,8] Quality of each of the included studies was evaluated by two coauthors independently. In the case of a disagreement, the primary author was approached, who then reviewed the study to reach a common consensus. Quality appraisal was done with the help of NIH Quality Assessment Tool for Case Series Studies whereby studies were rated as "good," "fair," or "poor" and NIH Quality Assessment Tool for Observational Cohort Studies.[8]

Out of 204 hospitalized patients, 68.1% received invasive mechanical ventilation without ECMO support, and 31.9% received invasive mechanical ventilation and were placed on ECMO. In both the groups, the number of males was comparatively higher than females (male-to-female ratio of 1.33:1 and 2.93:1 in patients in the non-ECMO group and ECMO group, respectively).[9,10,12,14–19,21–23,25–27]

The mean number of days to intubation from the date of hospitalization ranged from 1 to 10.6 days in 11 studies.[9–14,16–18,21–23,26,27] The mean number of days on invasive mechanical ventilation ranged from 10 to 37 days.[12-14,16,18,21,22] The mean number of days on ECMO ranged from 6 to 37 days.[9,14-16,18,22,25]

Patient comorbidities are detailed in Table 3. Hypertension (22.9%) and obesity (26.6%) were the most frequently reported comorbidities in the non-ECMO group and ECMO group, respectively.[9,10,14-19, 21-23,25-27] A graph visualizing the same is shown in Figure 2.

Seventy-six patients developed ARDS, of which 89.5% were intubated and mechanically ventilated and 10.5% were also placed on ECMO. Administration of prone positioning was reported in 33 patients (32.3%) out of a total of 101 patients.[9,10,20,21]

Pharmacological and supportive management of patients (Table 4) included antivirals, antibiotics, steroids, and hydroxychloroquine. Renal replacement therapy was administered to 41.0% (16) of the patients on ECMO out of a total of 39 patients in seven studies.[9,14,16,18,19,21,22,27]

At the end of the study period, 22.5% (46) of the patients were discharged and/or clinically improved, and 51.5% (105) of the patients died. Twenty-six percent (53) of the patients either deteriorated but remained alive or experienced no improvement in clinical condition at the end of the follow-up period. Primary and secondary outcomes of interest are detailed in Table 5. A 28-day follow-up was conducted for all included studies by contacting the respective corresponding authors. And 75.2% of those who died belonged to the group that received invasive mechanical ventilation without ECMO support, and the remaining 24.8% were on ECMO. The mortality rate in patients not on ECMO was 56.8% and 40% in those on ECMO. The male-to-female death ratio for patients who were on ECMO was 3:1 in the 10 studies that reported sex distribution.[9,10,12,14,16,18,19,21,22,25]

The mean number of days of hospitalization for survivors ranged from 17 to 53 days in six studies.[11,13,14,18,25,26] Most common complications in the non-ECMO group were multiorgan failure and thrombotic complications at 3.6% each, followed by septic shock (1.4%), bleeding (0.1%), and acute kidney injury (0.1%).[14,16] Most common complications in the ECMO group were septic shock and multiorgan failure at 10.9% each, followed by secondary infections (6.3%), other complications (6.3%), and bleeding (4.7%) (Figs 2 to 4).[10,14,15,18,19,22]

Discussion

As per the interim guidance released by WHO in January 2020 for the management of COVID-19, the use of extracorporeal life support (ECLS) was marked as a conditional recommendation that may be beneficial in selected patients. The WHO advised the referral of COVID-19 patients with refractory hypoxemia to specialists with expertise in ECLS.[5] ECLS has been shown to reduce mortality when compared with conventional treatment in the Middle East respiratory syndrome-related coronavirus infection.[28] This may point to the possible beneficial role that ECMO could play in the management of severe cases of COVID-19. However, the share of COVID-19 infected patients who are likely to develop respiratory infection severe enough to warrant ECMO use is currently not known.

As per the guidelines of the Extracorporeal Life Support Organization (ELSO), ECMO is recommended for adult hypoxic respiratory failure and persistent CO_2 retention with plateau pressure >30 cm H_2O (Pplat) in a patient on invasive mechanical ventilation. ECLS should be considered when PaO_2/FiO_2 <150 on FiO_2 >90% (mortality risk 50% or greater) and is indicated when PaO_2/FiO_2 <100 on FiO_2 >90% (mortality risk 80% or greater) within 6 hours of mechanically ventilating the patient. ELSO COVID-19 Interim guidelines recommend against initiation of ECMO until traditional

Table 1: Characteristics of primary studies

Primary author	*Year*	*Study design*	*Country of population*
Jacobs et al.[9]	2020	Case series	USA
Abou-Arab et al.[10]	2020	Case report	France
Young et al.[11]	2020	Case series	Singapore
Xiao et al.[12]	2020	Case series	China
Bhatraju et al.[13]	2020	Case series	USA
Zhang et al.[14]	2020	Case report	China
Zeng et al.[15]	2020	Case series	China
Taniguchi et al.[16]	2020	Case report	Japan
Wang et al.[17]	2020	Case series	China
Nakamura et al.[18]	2020	Case report	Japan
Ren et al.[19]	2020	Case series	China
Yang et al.[20]	2020	Case series	China
Barrasa et al.[21]	2020	Case series	Spain
Ma et al.[22]	2020	Case report	China
Zhang et al.[23]	2020	Case series	China
Zhou et al.[24]	2020	Retrospective cohort study	China
Shen et al.[25]	2020	Case series	China
Liu et al.[26]	2020	Case report	China
Ferrey et al.[27]	2020	Case report	USA

Table 2: Epidemiological features of patients in included studies

	Variables							
Studies	*Number of patients on invasive mechanical ventilation with or without ECMO*	*Mean age of patients placed on invasive mechanical ventilation with or without ECMO (n) (range)*	*Number of patients on invasive mechanical ventilation but not placed on ECMO (n)*	*Invasive mechanical ventilation but not placed on ECMO: Male (n)*	*Invasive mechanical ventilation but not placed on ECMO: Female (n)*	*Number of patients on invasive mechanical ventilation and ECMO (n)*	*Invasive mechanical ventilation and ECMO: Male (n)*	*Invasive mechanical ventilation and ECMO: Female (n)*
Jacobs et al.[9]	32	52.41	0	0	0	32	22	10
Abou-Arab et al.[10]	2	63	0	0	0	2	1	1
Young et al.[11]	1	Not reported	1	Not reported	Not reported	0	0	0
Xiao et al.[12]	1	78	0	0	0	1	1	0
Bhatraju et al.[13]	17	Not reported	17	Not reported	Not reported	0	0	0
Zhang et al.[14]	2	71	1	0	1	1	1	0
Zeng et al.[15]	12	50.9	0	0	0	12	11	1
Taniguchi et al.[16]	1	72	0	0	0	1	0	1
Wang et al.[17]	4	49.25	4	3	1	0	0	0
Nakamura et al.[18]	1	45	0	0	0	1	1	0
Ren et al.[19]	2	63	0	0	0	2	2	0
Yang et al.[20]	22	Not reported	16	Not reported	Not reported	6	Not reported	Not reported
Barrasa et al.[21]	45	63.2	44	24	20	1	1	0
Ma et al.[22]	3	63.3	2	2	0	1	0	1
Zhang et al.[23]	20	71.2	20	11	9	0	0	0
Zhou et al.[24]	32	56	29	Not report-ed	Not reported	3	Not reported	Not reported
Shen et al.[25]	5	(36–65)	4	2	2	1	1	0
Liu et al.[26]	1	48	1	1	0	0	0	0
Ferrey et al.[27]	1	56	1	1	0	0	0	0
Pooled analysis (*n*) (%)	204	Not applicable	140 (68.6)	44	33	64 (31.4)	41	14

ECMO: Extracorporeal membrane oxygenation

Table 3: Comorbidity in patients in included studies

Comorbidity in patients in included studies	*Comorbidity in patients on invasive mechanical ventilation but not on ECMO (n) (%)*	*Comorbidity in patients on ECMO (n) (%)*
Diabetes mellitus	13 (9.3)	14 (21.9)
Hypertension	32 (22.9)	5 (7.8)
Cardiovascular disease	10 (7.1)	6 (9.4)
Dyslipidemia	8 (5.7)	6 (9.4)
Obesity	23 (16.4)	17 (26.6)
Asthma	8 (5.7)	4 (6.3)
COPD	19 (13.6)	Not reported
Chronic kidney disease	1 (0.7)	2 (3.1)
Hyperthyroidism	8 (5.7)	1 (1.6)
Hypothyroidism	10 (7.1)	Not reported
Chronic liver disease	1 (0.7)	1 (1.6)
Cancer	1 (0.7)	3 (4.7)
Immunosuppression	3 (2.1)	Not reported
Others	15 (10.7)	1 (1.6)

ECMO: Extracorporeal membrane oxygenation; COPD: Chronic obstructive pulmonary disease

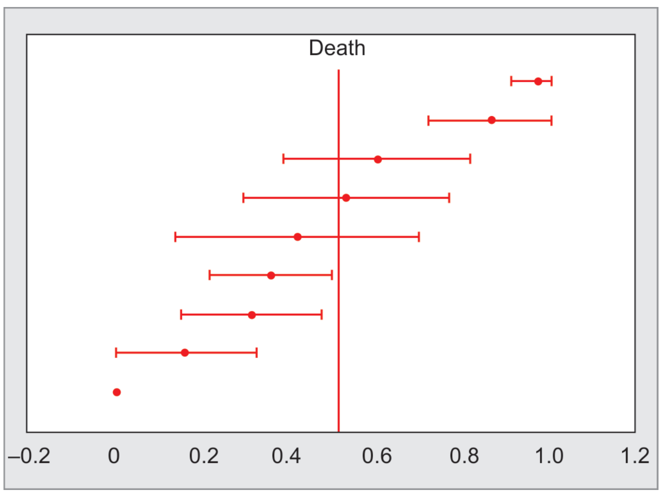


Fig. 2: Forest Plot for overall mortality in study population

management modalities for ARDS, in particular prone positioning, have been exhausted.[29]

The most frequently reported indication for invasive mechanical ventilation among the reviewed studies was respiratory failure and concomitant low oxygen saturation. Of note, several studies have been conducted on intensive care unit (ICU) versus non-ICU patients of COVID-19 and critically ill COVID-19 patients. However, within the wide spectrum of managing critically ill COVID-19 patients, the role of ECMO has not been explored in detail.[31]

In our pooled analysis, hypertension followed by obesity was the most frequently recorded comorbidities in mechanically ventilated patients without ECMO support, and these study findings have been observed by Richardson et al. as well.[32] We analyzed discharge and/or clinical improvement and mortality rates as primary outcomes in our study. Out of 204 intubated patients, 22.5% (46) of the patients were discharged and/or

Table 4: Pharmacological and supportive management of patients in included studies

Variables	*Pooled analysis (n)*
Pharmacological and supportive therapy	
Antivirals	
On invasive mechanical ventilation but not on ECMO (*n*)	53
ECMO (*n*)	25
Antibiotics	
On invasive mechanical ventilation but not on ECMO (*n*)	49
ECMO (*n*)	19
Steroids	
On invasive mechanical ventilation but not on ECMO (*n*)	46
ECMO (*n*)	18
Hydroxychloroquine	
On invasive mechanical ventilation but not on ECMO (*n*)	1
ECMO (*n*)	1
Renal replacement therapy	
On invasive mechanical ventilation but not on ECMO (*n*)	2
ECMO (*n*)	16

ECMO: Extracorporeal membrane oxygenation

clinically improved, and 51.5% (105) of the patients died. Also, 75.2% of those who died belonged to the group that received invasive mechanical ventilation without ECMO support, and the remaining 24.8% were on ECMO in addition to invasive mechanical ventilation. In the study conducted by Zhou et al., Fifty-seven percent of the nonsurvivors received invasive mechanical ventilation compared to 0.7% of the survivors.[24] Similarly, in a study based out of the New York City area, out of 5,700 patients admitted to the hospital for COVID-19 infection, 51% of those who died were intubated and mechanically ventilated compared to 1.9% of those who were discharged. In the same study, 88.1% of the intubated patients who had an outcome at the end of the study, that is, discharged or dead, died and 11.9% were discharged.[32] In our systematic review, 51.5% of the intubated patients died. The data reported to date point to the high mortality associated with critically ill COVID-19 patients.[24,32]

Currently, ECMO use is restricted to few centers across the globe as it is a resource-intensive and highly specialized modality of life support with a significant risk of complications, such as bleeding and infections. Despite the reported mortality benefits, safety, and efficacy of using ECMO in ARDS, a pandemic such as the current one calls for careful and prudent resource allocation.[6,33-35]

Centralization is essential for providing specialized care and also ensures a high patient volume. As per the "Conventional ventilatory support vs Extracorporeal membrane oxygenation (ECMO) for Severe Adult Respiratory failure" (CESAR) trial, patients who were treated in specialized units had better outcomes regardless of whether they were administered ECMO or not.[36] Recent evidence also suggests that high patient volume has been associated with improved patient outcomes.[37,38]

Amidst a pandemic, training personnel to provide expert care while ensuring strict infection control measures is difficult.

Table 5: Primary and secondary outcomes

Variables	*Pooled analysis (n) (%)*
Complications	
Secondary infection	
On invasive mechanical ventilation but not on ECMO (*n*)	1(0.1)
ECMO (*n*)	4 (6.3)
Septic Shock	
On invasive mechanical ventilation but not on ECMO (*n*)	2 (1.4)
ECMO (*n*)	7 (10.9)
Multiorgan failure	
On invasive mechanical ventilation but not on ECMO (*n*)	5 (3.6)
ECMO (*n*)	7 (10.9)
Bleeding	
On invasive mechanical ventilation but not on ECMO (*n*)	1 (0.1)
ECMO (*n*)	3 (4.7)
Thrombotic complications	
On invasive mechanical ventilation but not on ECMO (*n*)	5 (3.6)
ECMO (*n*)	1 (1.6)
Acute kidney injury	
On invasive mechanical ventilation but not on ECMO (*n*)	1 (0.1)
ECMO (*n*)	1 (1.6)
Others	
ECMO (*n*)	4 (6.3)
Outcome	
Discharged and/or clinically improved	46 (22.5)
Death (*n*)	105 (51.5)
Death in patients on invasive mechanical ventilation but not on ECMO (*n*)	79 (38.7)
Death in patients on ECMO (*n*)	26 (12.7)

ECMO: Extracorporeal membrane oxygenation

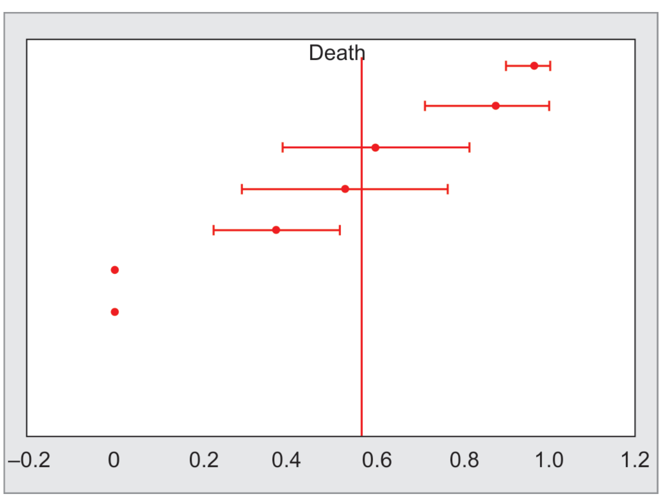


Fig. 3: Forest Plot for Mortality in Non ECMO group

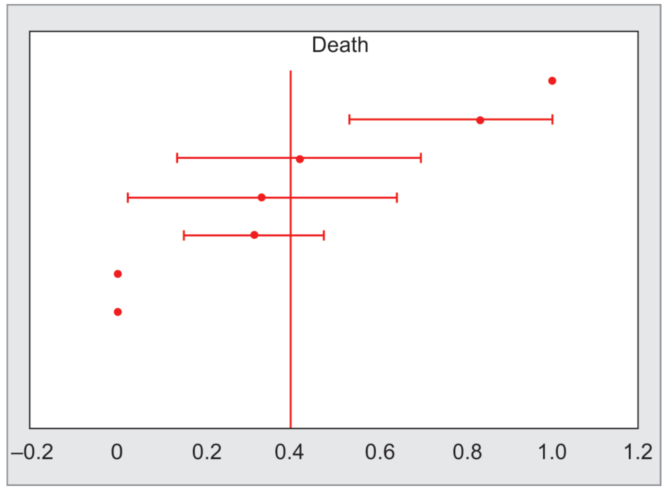


Fig. 4: Forest Plot_death in ECMO group

It is important to weigh the risk-to-benefit ratio on a case-to-case basis before administering ECMO by accounting for patient-specific comorbidities, such as renal and cardiac dysfunction, and risk of complications like secondary infections, septic shock, presence of multiorgan failure, and bleeding or thrombosis.[30] In particular, ECMO-assisted cardiopulmonary resuscitation in a COVID-19 patient is a high-risk procedure that places healthcare professionals at significant risk of acquiring the infection in the setting of poor patient outcomes.[15,30,31]

Although guidelines provide recommendations about the ideal time for initiating ECMO support in adult hypoxic respiratory failure patients, the guidance specifically for severely ill COVID-19 patients is not available. Whether ECMO reduces mortality in population subsets infected with COVID-19 can be ascertained only with the help of large multicenter prospective studies.[29,30]

Study Limitations

Despite performing a thorough literature search in large databases, conducted by two investigators independently and followed by meticulous cross-referencing, we acknowledge that a relevant study could have been missed. Since there was a large heterogeneity in the reporting of results and population characteristics by primary studies, only a few studies could be included for any particular outcome analysis. Moreover, being a systematic review, limitations inherent to the primary studies, and bias arising from the search and selection processes are applicable. Although, to the best of our knowledge, this is the first systematic review and meta-analysis evaluating the outcome of COVID-19 patients placed on ECMO, it is limited by small sample size.

Clinical Significance

Mortality in COVID-19 is often attributed to progressive hypoxemic respiratory failure. Many researchers have reported the benefits of using ECMO for patients with a more severe form of infection. However, the development and implementation of concrete and uniform management guidelines remain yet to be accomplished.

Conclusion

The use of ECMO is applicable to the management of life-threatening respiratory failure. However, its utility during a pandemic is uncertain as it is a resource-intensive modality, especially when the mortality rate in severely ill patients infected with COVID-19 virus is already known to be high. Therefore, the benefit should be assessed on a case-to-case basis. Moreover, centralization is essential for providing specialized care and ensuring a high patient volume.

Highlights

This is the first systematic review studying ECMO and invasive mechanical ventilation use in COVID-19 patients. This meta-analysis includes a heterogeneous patient population belonging to different countries and the inherent epidemiological characteristics of the same.

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