The use of extracorporeal membrane oxygenation in COVID-19: a systematic review

Marius Andrei Zavalichi[1], Georgiana Ionescu[1]*, Cătălina Marina Arsenescu Georgescu[2], Adelina Mihaescu[3,4], Carmen Diana Cimpoesu[5], Gabriel Cimpoesu[6], Simona Daniela Zavalichi[7], Cristian Stătescu[1], Atalay Demiray[8], Mehmet Kanbay[8], Adrian Covic[9], Ionuț Nistor[9,10]

[1]Cardiology Department, Cardiovascular Diseases Institute "Prof. Dr. George I.M. Georgescu", University of Medicine and Pharmacy „Grigore T.Popa", Iași, Romania
[2]Cardiology and Internal Medicine Department, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania
[3]Department of Internal Medicine II – Division of Nephrology, "Victor Babeș" University of Medicine and Pharmacy, Timisoara, Romania
[4]Centre for Molecular Research in Nephrology and Vascular Disease, Faculty of Medicine, "Victor Babeș" University of Medicine and Pharmacy, Timisoara, Romania
[5]University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania
[6]Citadin SA, Iasi, Romania
[7]Physical Medicine and Rehabilitation Department, Rehabilitation Clinical Hospital, Iasi, Romania
[8]Department of Medicine, Koc University School of Medicine, Istanbul, Turkey
[9]Nephrology Department, "C. I. Parhon" Hospital, University of Medicine and Pharmacy, "Grigore T. Popa", Iasi, Romania
[10]Research Methodology and Evidence Based Medicine Center, University of Medicine and Pharmacy „Grigore T.Popa", Iasi, Romania

***Corresponding author:**
Georgiana Ionescu MD
Cardiology Department
Cardiovascular Diseases Institute "Prof. Dr. George I.M. Georgescu"
Iasi, Romania
E-mail: georgianaionescu944@gmail.com

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Abstract

Introduction: The COVID-19 pandemic represents a major worldwide challenge, with a great impact on health systems and economic mechanisms. SARS-CoV-2, the pathogenic agent that generates COVID-19, creates a wide variety of organ dysfunctions, from acute respiratory distress syndrome (ARDS) to acute myocardial infarction or pulmonary embolism. Mechanical circulatory support devices such as extracorporeal membrane circulatory oxygenation (ECMO) have shown their efficacy in maintaining organ perfusion in respiratory and cardiac impairments. With this review, we aimed to assess the impact of ECMO use in COVID-19 patients with ARDS.

Material and methods: We performed a systematic review to find studies using ECMO in COVID-19. Comorbidities, side effects, and survival rate to discharge were analysed. The literature search was done using PubMed/MEDLINE, Web of Science, Embase (Elsevier), the Cochrane Central Register of Controlled Trials (Wiley) and clinicaltrials.gov databases (inception (December 2019) to October 16, 2021), by 2 authors.

Results: We included 33 studies from 10 countries with a total of 4760 patients receiving ECMO for COVID-19. The survival rate varied from 9% to 90.6% at discharge. The most serious adverse events were acute kidney injury (up to 87%), major bleeding (up to 92.1%), strokes or cerebral haemorrhage (up to 34%). Other complications such as pulmonary embolism, peripheral bleeding, or sepsis had a major impact on survival rates.

Conclusions: ECMO in COVID-19 patients may be a useful rescue therapy instrument, but due to the great variability of studies and still unknown mechanisms and effects of SARS-CoV-2, further studies need to be done.

Key words: COVID-19, SARS-CoV-2, acute respiratory distress syndrome, extracorporeal membrane circulatory oxygenation, survival, mechanical circulatory support, extracorporeal life support.

Introduction

The severity of COVID-19, a major challenge for worldwide nations, may vary from mild pneumonia to acute respiratory distress syndrome (ARDS) complicated by respiratory failure, septic shock, or multiple organ dysfunction [1], with mortality rates of 23.9% in critically ill patients [2], despite new treatment protocols [3]. Also, cardiovascular impairments such as fulminant myocarditis or major vascular events may appear [4]. These potentially fatal complications require an immediate therapeutic strategy, with extracorporeal life support such as extracorporeal membrane oxygenation (ECMO) to stabilize these patients' critical condition.

ECMO is a mechanical support device similar to cardiopulmonary bypass, and it has two main types, i.e. veno-arterial ECMO (V-A ECMO) and veno-venous ECMO (V-V ECMO), with sometimes the combination venous-arterial-venous ECMO (V-A-V ECMO).

The Extracorporeal Life Support Organization (ELSO) mentions a couple of criteria for considering V-V ECMO in hypoxic respiratory failure: PaO_2/FiO_2 ratio lower than 150, on FiO_2 over 90% and a Murray score of 2–3, or PaO_2/FiO_2 under 100 on FiO_2 over 90% and a Murray score 3–4 despite optimal care for more than 6 h [5].

The main advantages of V-V ECMO therapy are better oxygenation, lung protection during ventilation without severe hypercapnia and respiratory acidosis providing safer transportation [6]; V-A ECMO is useful in cases of cardiac involvement as it has been described in a recent systematic review which included 9 studies with a total of 1,998 adult patients receiving V-A ECMO for acute myocardial infarction-induced cardiogenic shock. The survival rate varied from 30.0% to 79.2% at discharge and from 23.2% to 36.1% at 12 months. ECMO therapy represents a temporary support that provides benefits compared to standards of care, being an upgradable device for advanced life support that could assure a higher survival rate [7]. ELSO published the most recent COVID-19 consensus which provides substantial contraindications by adding specific technical measures for the patient and the medical team [8]. The most frequent complication of ECMO is bleeding, with a frequency of 29.3% reported in a systematic review, followed by local infections (9.9%), pulmonary bleeding, and intracerebral haemorrhage [9].

The CESAR trial showed a 6-month survival rate of 63%, demonstrating the reliability of ECMO for treating ARDS in (H1N1) influenza epidemics when lung ventilation protocols failed [10]. Similarly, other studies showed survival rates of 76.3% [11], 78% [12], 71% [13], or even a survival to discharge rate of 100% [14] when compared to standard care therapy. Recent recommendations of ELSO [15] indicate ECMO usage in patients with high mortality risk, with the indications of the EOLIA trial [16] to define severe ARDS that may require mechanical support. Some recent studies recommended use of ECMO as salvage therapy in patients with severe COVID-19 infections.

Hospitalised patients with coronavirus disease 2019 (COVID-19) have a high mortality rate. There are many published randomised controlled trials for COVID-19 treatments [17]. The use of antivirals or other repositioning drugs is essential for clinical improvement and survival. In the absence of a specific treatment, *in vitro* and *in vivo* studies have been proposed to use existing drugs such as tocilizumab (monoclonal antibodies), remdesivir (antiviral), chloroquine and hydroxychloroquine (antimalarial), lopinavir and ritonavir (antiretrovirals), dexamethasone (glucocorticoid), and convalescent plasma (neutralizing antibody) [18]. Several studies have stated that antivirals drugs such as remdesivir, favipiravir, and lopinavir/ritonavir may potentially inhibit the virus from spreading to the host. In a systematic review which pooled data from 15 studies, involving a total of 5310 patients, the results showed that remdesivir has some potential benefits for hospitalized COVID-19 patients, as seen from clinical improvements such as faster recovery time, shorter duration of hospitalization, and fewer respiratory side effects among COVID-19 patients. However, the impact of remdesivir in reducing mortality remains uncertain. Treatment with favipiravir has shown promising improvement in the clinical status of COVID-19 patients, although the results suggested no significant differences in some clinical parameters such as length of hospitalizations and clinical recovery. Furthermore, the use of lopinavir/ritonavir in COVID-19 patients showed no significant clinical improvement compared to standard care with notable adverse effect reactions [19].

The survival of critical ill patients with COVID-19 has been reported variously. The application of scoring systems can facilitate the effective evaluation by physicians to screen severe patients. At present, there are no specific scoring systems for the evaluation of COVID-19 patients. However, scoring systems such as the Sequential Organ Failure Assessment (SOFA) score can help emergency or critical care physicians for prognosis and predicting mortality [20]. Besides the SOFA score, the Acute Physiology and Chronic Health Evaluation (Apache II) score was designed to measure the severity of disease of patients admitted to the ICU and to predict mortality [21]. The Murray Score is used to grade the severity of lung injury in acute respiratory distress syndrome (ARDS) [22].

With this background in mind, this systematic review aimed to evaluate the effects of ECMO in patients with severe COVID-19 infection and respiratory support.

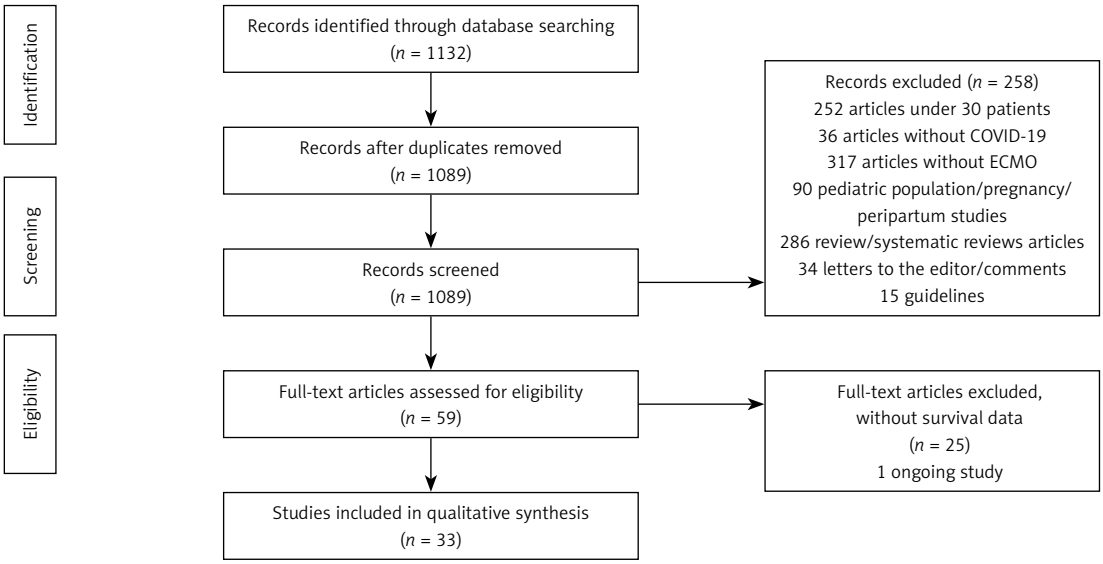

Figure 1. Details of study selection process for the meta-analyses as shown by PRISMA flow chart

Material and methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide reporting of this study [23]. The detailed search strategy is shown in Figure 1.

Protocol and registration

This protocol has not been registered in the PROSPERO database of systematic review protocols.

Data sources/search strategy

We have searched PubMed/MEDLINE, Web of Science, Embase (Elsevier), the Cochrane Central Register of Controlled Trials (Wiley) and clinicaltrials.gov databases (inception (December 2019) to October 16, 2021) without language restrictions. Hand searching for relevant articles was done.

Key words for the search

During our search, we used keywords for the population of interest and intervention of interest which are shown in Table I. Articles that were considered suitable by title and a thorough abstract reading were included for full-text evaluation. Referenced articles in the selected studies were also read thoroughly for any significance.

Study selection. Inclusion and exclusion criteria

All observational studies and randomized clinical trials for COVID-19 adults treated with ECMO were searched. We reported data on the impact of ECMO on survival, mortality, adverse events related to ECMO usage, and associated comorbidities of patients with COVID-19 on ECMO.

No data about prior vaccination were registered in the included studies.

We only included studies with more than 30 patients. We excluded any animal, paediatric (< 18 years)/pregnancy/peripartum population studies, any studies under 30 patients or without COVID 19, studies without ECMO, systematic reviews articles, letters to the editor/comments or guidelines.

Data extraction and synthesis

Data extraction was done independently by two authors (M.A.Z. and G.I.), using standardized data extraction forms. Extracted data included study outcomes, study protocol, and demographic data.

Table I. Key words used for search strategy

Key words
Extracorporeal membrane oxygenation
ECMO
Veno-venous extracorporeal membrane oxygenation
Veno-venous ECMO
V-V ECMO
Veno-arterial ECMO
V-A ECMO
Mechanical circulatory support
Extracorporeal life support
ECLS
Coronavirus disease 2019
COVID-19
SARS-COV-2
Acute respiratory distress syndrome
ARDS
Survival

Quality assessment

Risk of bias. Quality of the selected studies was independently evaluated by 2 reviewers (M.A.Z and G.I.), using the Newcastle-Ottawa scale (NOS); according to the NOS, 3 methodological categories were used for assessment: selection (score 0–4), comparability (score 0–2), and outcome (score 0–3). Quality was considered high if the score was 7–9, intermediate if the score was 4–6, and low if the score was 0–3. Disagreements were resolved by consensus [24].

Results

1132 records initially resulted as potentially relevant articles. After removing duplicates and performing an analysis, a total of 59 full-text articles were thoroughly analysed and 33 articles were included.

We included three studies from France, three studies from the People's Republic of China, 12 studies from the United States of America, 6 studies from United Kingdom, 3 studies from Germany, 2 studies from Italy, 1 study from Finland, 1 study from the Netherlands, 1 study from Poland, and 1 study from Japan.

V-V ECMO was used in 20 studies, while V-A ECMO was performed in 13 studies, in cases of cardiac involvement or pulmonary embolism.

The main characteristics of the included studies are presented in Table II.

Baseline characteristics of included studies

The median age was between 43.2 [25] and 62 [26].

The most frequent comorbidities in COVID-19 patients treated with ECMO were hypertension, which varied from 21% [27] to 53.5% [28], and diabetes mellitus, which varied from 8% [27] to 39.6% [29]. Also, chronic obstructive pulmonary disease or asthma varied between 1.1% [30] and 18.9% [31].

Body mass index was between 28.9 kg/m^2 [32] and 36 kg/m^2 [33]. The baseline characteristics of the studies are presented in Table III [25–57].

ECMO survival rate

Survival at discharge was reported in all studies, with the lowest rate encountered in Weir-McCall *et al*. [32] (9%) and the highest in Garfield *et al.* [31], where 90.6% of the patients survived from decannulation and 84.9% at 6 months.

Tabatabai *et al.* reported that 82.5% completed ECMO therapy and 17.5% remained on ECMO at data collection; only 54.5% survived, and 45.5% died [25], while Yang *et al.* reported 13.7% survivors: 9.6% of patients were discharged home, 4.1% were transferred to general wards; 5.5% of patients were still in ICUs on invasive ventilator including 2.7% on ECMO at data collection; 63% died by 30 days and 80.8% died by 60 days [26].

In Raasveld *et al.* 52% of the patients were weaned off ECMO, and after 28 days the survival rate was 63% [27]. Shih *et al*. reported 33 survivors (62.3%) with a survival rate at 30 days of 100%, and a survival rate at 60 days of 100% [29], while Supady *et al.* reported a survival rate at 30 days of 54.3%, and at 60 days of 45.7% [34]. Fang *et al*. reported that 30.7% patients were weaned off ECMO, of whom 17% were discharged and 9.1% remained in hospital at data collection with a 120-day in-hospital survival of 25.7% and mortality rate of 74.3% [30]. A high percentage of survivors was seen in Doyle *et al*. [35], where 74%, 37.7 out of 51 patients, were successfully weaned off and discharged after ECMO, with 1 patient still on ECMO at data collection. Schmidt *et al.* reported 53.5% survivors, 2% in ICU weaned off and 2% still on ECMO, with a survival rate after 90 days of 58% [36], while Arachchillage *et al.* reported a 70.4% survival rate after 180 days [37].

Saeed *et al.* reported 160 of 292 patients who were weaned off ECMO of whom 135 (46%) were discharged and 25 (9%) remained in hospital; 19 (6%) were still on ECMO at data collection and the cumulative incidence on in-hospital survival rate was 58% [38], with a similar survival rate in Nguyen *et al*., 54.1% [28].

Successful V-V and V-A ECMO weaning with subsequent survival was reported to be less than 50% in most of the implanting centres in Onorati *et al*. [39].

Loforte *et al*. [40] reported a primary configuration with 67 patients on V-V ECMO, 4 patients with multiorgan failure who were upgraded to V-A-V ECMO and 5 patients with a second configuration of V-A ECMO. 36.6% of patients survived, 54.9% died on ECMO including the second configuration cases, and 8.5% died after ECMO removal.

Bergman *et al.* reported a survival rate at 60 days of 65.2% [41], while Li *et al.* reported a 29% survival rate after 60 days [42]. Biancari *et al.* reported that after 6 months the survival rate was 46.9% [43].

Also, Mustafa *et al.* reported that 71% were decannulated from ECMO of whom 67.5% were discharged, 8% remained hospitalized at data collection and 1 received a double lung transplant before discharge [44]. Ogura *et al.* reported a survival rate of 66.8% [45]. On the other hand, Cho *et al.* reported that ECMO therapy increased both the instantaneous and cumulative hazard of death (HR = 1.78) [46]. The remaining studies reported a survival rate between 25% in Zaaqoq *et al.* [47], and 67.4% in Zhang *et al.* [55]. Lebreton *et al.* re-

Table II. The main characteristics of the included studies

Study	Country	Year	Patients on ECMO	ECMO type	Survival rate
Tabatabai *et al.* [25]	United States of America	2020	40	V-V	82,5% completed ECMO therapy and 54.5% survived 17.5% remained on ECMO at data collection
Yang *et al.* [26]	China	2020	73	V-V	13.7% survivors 5.5% still in ICU including 2.7% on ECMO at data collection
Raasveld *et al.* [27]	Netherlands	2020	71	66 V-V 3 V-A 1 V-V-A	52% weaned off, 28 days mortality rate was 37%/ 28 days survival rate was 63%
Nguyen *et al.* [28]	United States of America	2020	1182	NA	54.1% survivors In-hospital survival 54.1%
Shih *et al.* [29]	United States of America	2020	53	49 V-V 4 V-A	62.3% survivors 30 days survival rate 100% 60-days survival rate 100%
Fang *et al.* [30]	China	2020	88	V-V (V-A or V-A-V excluded)	30.7% of patients weaned off ECMO 17% were discharged, 9.1% remained in hospital at data collection 120-day in hospital mortality rate-74.3%
Garfield *et al.* [31]	United Kingdom	2020	53	VV V-A was excluded	90.6% survived from decannulation 6 months survival rate 84.9%
Weir-McCall *et al.* [32]	United Kingdom	2019–2020	64	V-V	9% discharged, 20% remained on ECMO at data collection, 14% off ECMO but remained on ventilator support, 13% remained on non-invasive ventilation, 11% remained in hospital on oxygen therapy, 5% remained in hospital without oxygen therapy
Bissell *et al.* [33]	United States of America	2020	33	V-V	51.5% survivors 48.5% ICU mortality rate
Supady *et al.* [34]	Germany	2020	127	V-V	After 30 days 54.3% survived After 60 days 45.7% survived deaths by day-30 was 45.6%
Doyle *et al.* [35]	United Kingdom	2020	51	V-V	74% survivors 1 patient still on ECMO at data collection
Schmidt *et al.* [36]	France	2020-2021	159	154 V-V 3 V-A 1 V-AV	53.5%, survivors 90 days survival rate was 58%
Arachchillage *et al.* [37]	United Kingdom	2020	152	V-V	70.4% survived at 180 days
Saeed *et al.* [38]	United States of America	2020	292	280 V-V 10 V-A 2 VA-V	46% discharged/transferred alive 9% weaned off ECMO, but remained in hospital 6% still on ECMO at data collection 90 days in-hospital mortality was 42%
Onorati *et al.* [39]	Italy	2020	228	203 V-V 25 V-A	Successful ECMO weaning with subsequent survival less than 50% in most of the implanting centers
Loforte *et al.* [40]	Italy	2020	71	Primary configuration 67 V-V 4 V-A-V Second configuration 5 V-A	36.6% survived 54.9% died on ECMO including the secondary V-A ECMO cases 8.5% died after ECMO removal

Table II. Cont.

Study	Country	Year	Patients on ECMO	ECMO type	Survival rate
Bergman *et al.* [41]	United States of America	2020	46	V-V V-A-V	60 days survival rate was 65.2%
Li *et al.* [42]	China	2019–2020	31	V-V	26% weaned off ECMO 60 days mortality rate was 71%
Biancari *et al.* [43]	Finland	2020	132	122 V-V 10 V-A Changed configuration 8 V-V, 3 V-A, 5 V-A-V	At 6 months 46.9%survival rate
Mustafa *et al.* [44]	United States of America	2020–2021	80	V-V	71% weaned off, 67.5% discharged 1 received a double lung transplant before discharged
Ogura *et al.* [45]	Japan	2020	187	V-V (V-A or V-A-V were excluded)	66.8% weaned off ECMO
Cho *et al.* [46]	United States of America	2020	283	94% V-V	ECMO use (HR = 1.78) increased the instantaneous and cumulative hazard of death
Zaaqoq *et al.* [47]	United Kingdom	2020	232	V-V	25% discharged from hospital 4% remain in the hospital on data collection
Suwalski *et al.* [48]	Poland	2020	75	74 V-V 1 V-A	38.6% survivors 8 listed for lung transplantation; of those, 4 underwent successful
Jacobs *et al.* [49]	United States of America	2020	200	188 V-V 12 V-A	45% survivors 55% died
Kunavarapu *et al.* [50]	United States of America	2020	52	V-V	56% survivors
Shaefi *et al.* [51]	United States of America	2020	190	V-V	60% survivors, discharged 4.7% hospitalized at data collection
Bermea *et al.* [52]	United States of America	2021	33	V-V	48.5% discharged, 12.1% had ongoing care
Fröhlich *et al.* [53]	Germany	2020	53	NA	64.2% survivors
Luyt *et al.* [54]	France	2020	50	V-V	66% survivors
Zhang *et al.* [55]	United Kingdom	2020	43	V-V	67.4% survived, discharged 14 died – 12 on ECMO, 2 after decannulation
Supady *et al.* [56]	Germany	2020	34	V-V	Survival at 30-days –18% with cytokine adsorption and 76% without
Lebreton *et al.* [57]	France	2020	302	288 V-V 11 V-A 3 V-A-V	46% – 90 days after ECMO

ported a 46% survival rate at 90 days after completion of ECMO [57].

Severity of illness parameters, treatments, ECMO duration, hospitalization time

In Table IV we described the parameters of the severity illness of patients with COVID-19. We reported that the severity scores correlated with mortality. SOFA, APACHE II and Murray risk scores have been reported at ICU admission in 17 studies. Doyle *et al.* [35] reported SOFA score 6, which means a risk of mortality < 10%, with a survival rate of 74%. Raasveld *et al.* [27], Fang *et al.* [30], Bergman *et al.* [41], Li *et al.* [42], Zaaqoq *et al.* [47], Kunavarapu *et al.* [50], Zhang *et al.* [55] and Supady *et al.* [34, 56] have reported a similar SOFA score between 7 and 9, associated with a 15–20%

Table III. Baseline characteristics of included studies

Study	Male	BMI	Arterial hypertension	Diabetes mellitus	Chronic respiratory disease, COPD, or asthma
Tabatabai *et al.* [25]	80%	34 (7.1)	22.5%	30%	10%
Yang *et al.* [26]	63%	NA	37%	17.8%	6.8% COPD
Raasveld *et al.* [27]	80%	29.2 (26.1–32.1)	21%	8%	10% asthma/6% COPD
Nguyen *et al.* [28]	71.4%	NA 58.3% obesity	53.5%	36%	17.9% chronic pulmonary disease
Shih *et al.* [29]	67.9%	33.6 (30.6–37.9)	52.8%	39.6%	7.5% COPD
Fang *et al.* [30]	63.6%	NA	39.8%	20.5%	1.1% chronic lung disease
Garfield *et al.* [31]	73.6%	29.4 (25.6–34.2)	24.5%	17%	18.9% asthma. 0 COPD
Weir-McCall *et al.* [32]	77%	28.9 ±7.0	23%	25%	14% – 8 asthma, 1 other
Bissell *et al.* [33]	60.6%	36 (10)	NA	NA	NA
Supady *et al.* [34]	78.7%	29 (26–35)	NA	NA	10% chronic lung disease
Doyle *et al.* [35]	74.5%	NA	NA	NA	NA
Schmidt *et al.* [36]	72%	30.8 (27.7–35.1)	40%	34%	15%
Arachchillage *et al.* [37]	75%	NA	28.9%	24.3%	15.8%
Saeed *et al.* [38]	72.2%	32 (29–37)	41%	31%	3% chronic respiratory disease
Onorati *et al.* [39]	NA	NA	NA	NA	NA
Loforte *et al.* [40]	85.9%	30.2 (24.1–36.3)	43.7%	16.9%	7%
Bergman *et al.* [41]	82.6%	31.7 (6.6)	45.7%	39.1%	8.7%
Li *et al.* [42]	61%	NA	23%	16%	NA
Biancari *et al.* [43]	82.5%	30.9 (6.6); 56 – BMI > 30 kg/m^2	28.8%	22%	9.2%
Mustafa *et al.* [44]	76.3%	34.1 (0.8)	NA	NA	NA
Ogura *et al.* [45]	83.4%	NA	NA	NA	NA
Cho *et al.* [46]	70%	NA	NA	NA	NA
Zaaqoq *et al.* [47]	69%	30 (27–36)	41%	25%	NA
Suwalski *et al.* [48]	77.3%	NA	NA	NA	NA
Jacobs *et al.* [49]	69%	NA 64% obesity	47%	38%	16.5% asthma
Kunavarapu *et al.* [50]	67.3%	32 (6.0)	46.2%	30.8%	13.5% asthma
Shaefi *et al.* [51]	72.1%	32.7 (29.1–38)	NA	NA	6.8% chronic lung disease
Bermea *et al.* [52]	NA	NA	NA	NA	NA
Fröhlich *et al.* [53]	67.9%	NA	NA	NA	NA
Luyt *et al.* [54]	72%	NA	NA	NA	NA
Zhang *et al.* [55]	76.7%	29 (27–34)	23.3%	18.6%	11.6% asthma
Supady *et al.* [56]	73.5%	29.5	47%	23.5%	11.76%
Lebreton *et al.* [57]	78%	29.7 (26.8–33.5)	34%	29%	11%

mortality risk, with a survival rate more than 60%. Tabatabai *et al.* [25], Schmidt *et al.* [36], Biancari *et al.* [43], Luyt *et al.* [54] and Lebreton *et al.* [57] have reported a SOFA score between 10 and 12, associated with a mortality risk of 40–50%; the survival rate of these studies was almost 50%. The APACHE II score was reported in Yang *et al.* [26] as 19, Weir-McCall *et al.* [32] as 13.9, Supady *et al.* [34] as 17, Doyle *et al.* [35] as 14, Li *et al.* [42] as 12.4, and these studies reported survival rates between 9% in Weir-McCall *et al.* [32] and 74% in Doyle *et al.* [35]. The Murray score > 3 was reported in Fang *et al.* [30] and Zhang *et al.* [55], with survival rates of 30.7% and 67.4%, respectively.

In these studies, we observed a tendency to acidosis (Table IV).

21 studies reported mechanical ventilation parameters before ECMO initiation: Tabatabai

Table IV. Severity of illness, treatment/intervention, ECMO duration and hospital time course

Study	Severity of illness parameters, mean	Treatments received (*n* %)	Days from symptom to mechanical ventilation	Days from intubation to cannulation	ECMO duration [days]	Days on ICU/ Hospital length of stay
Tabatabai *et al.* [25]	SOFA 9.6 (3.0) pH 7.3 (0.1) $PaCO_2$ (mm Hg) 63.9 (18.0) PaO_2/FIO_2 ratio, (mm Hg) 71.1 (18.7) P_{IP} (cm H_2O) 38 (7.5) PEEP (cm H_2O) 15.6 (3.5) MAP (cm H_2O) 25.1 (4.8)	Remdesivir 27.5% Tocilizumab 30% Methylprednisolone (Meduri Protocol) 67.5% Steroids for inflammation 20% Convalescent Plasma 55% Stem cells 12.5%	NA	3.4 (2.7)	29.1 (15.9)	NA/55.6 (22.5)
Yang *et al.* [26]	APACHE II 19 (16–21) pH 7.31 (7.24–7.41) $PaCO_2$ (mm Hg) 63.9 (50–85) PaO_2, mm Hg 70 (54–72) PaO_2/FIO_2 ratio, (mm Hg) 72 (60–85.8) PEEP, cm H_2O 10 (8–12)	Steroid therapy 78.6% Convalescent plasma 14.3%	20 (17–29)	1.5 (0–6)	18.5 (12–30)	NA
Raasveld *et al.* [27]	SOFA 9 (7–12) pH 7.35 (7.22–7.42) PCO_2, kPa 8 (6.6–10.1) PO_2, kPa 8 (6.8–9.3) PaO_2/FIO_2-ratio, mm Hg 58 (46–76)	Lopinavir/ritonavir 20% Remdesivir 7% Tocilizumab 13% Anti-IL 1 4% Hydroxychloroquine 66% IV Ig 3% Convalescent plasma 0% Plasmapheresis 1% Cytokine absorber 18%	14 (10–18)	5 (3–10)	13 (7–20)	NA
Nguyen *et al.* [28]	NA	NA	NA	NA	NA	29.1 ±17.3/ 37.1 ±24.9
Shih *et al.* [29]	Critically ill, intubated 100%	NA	3.5 (1–6.8)	NA	14 (9–30)	27 (23–58)/ 37 (27–62)
Fang *et al.* [30]	SOFA score 8 (6–10) Murray score 3 (2.70–3.3) pH < 7.35 38.5% $PaCO_2$ mm Hg 58.65 (42.85–71.83) PaO_2/FIO_2, mm Hg < 80 41.7% PEEP cm 10 (8–11) PaO_2/FIO_2, mm Hg 88.75 (65.79–128.27)	Anti-viral treatment 59.1% Anti-microbial treatment 98.9% Anti-fungi treatment 65.9% Corticosteroids 64.8% IV Ig 56.8% Convalescent plasma 21.6%	20 (15–26)	3 (1–7)	13 (5.75–24.25)	25 (10.75–40)/ 30.5 (13.75–50)

Table IV. Cont.

Study	Severity of illness parameters, mean	Treatments received (*n* %)	Days from symptom to mechanical ventilation	Days from intubation to cannulation	ECMO duration [days]	Days on ICU/ Hospital length of stay
Garfield *et al.* [31]	pH 7.28 (7.18–7.38) $PaCO_2$ (kPa) 8.4 (6.8–10.3) PaO_2/FIO_2 ratio (kPa) 9.3 (8.1–10.7) PEEP cm H_2O 12.5 (10–15)	NA	NA	3.5 (2.0–6)	18 (12–30)	NA
Weir-McCall *et al.* [32]	APACHE score 13.9 ±6.1 PaO_2, kPa 12.8 ±8.9	NA	NA	NA	NA	NA
Bissell *et al.* [33]	NA	NA	NA	NA	16 (25)	25 (32)/33 (35)
Supady *et al.* [34]	SOFA 9 (7–10) APACHE II 17 (12–21) pH 7.3 (7.2–7.5) pCO_2 [mm Hg] 57 (45–67) pO_2 [mm Hg] 64 (52–76) PaO_2/FIO_2 [mm Hg] 70.2 (57.1–97.1) PEEP [mbar] 14 (10–16)	NA	NA	5 (2–9)	NA	NA
Doyle *et al.* [35]	SOFA 6 (3–16) APACHE II 14 (5–22)	NA	NA	NA	13 (8–21)	NA
Schmidt *et al.* [36]	SOFA 11 (9–13) pH 7.32 (7.25–7.39) $PaCO_2$, mm Hg 56 (49–65) PaO_2, mm Hg 63 (54–70) PaO_2/FIO_2 60 (54–69)	Lopinavir/ritonavir 13% Remdesivir 11% Tocilizumab 6% High-dose corticosteroids 6% Dexamethasone, ≤ 6 mg/day 46%	10 (7–13)	4 (1–7)	18 (5–35)	50 (32–75)/ 74 (49–154)
Arachchillage *et al.* [37]	$PaCO_2$ (kPa) 7.8 (6.4–9.2) PaO_2/FIO_2 ratio (kPa) 9.4 (8.3–10.7)	Tocilizumab 5.3% Steroids 59.9% IV Ig 3.3% Plasmapheresis 9.2%	NA	1–6 days 71.1% ≥ 7 days 28.9 %	17.5 (11–30)	NA
Saeed *et al.* [38]	pH 7.31 (7.21–7.38) $PaCO_2$, mm Hg 56 (45-71) PaO_2/FIO_2 77 (63–101)	NA	2 (1–7)	3 (1–6)	15 (9–25)	NA
Onorati *et al.* [39]	NA	NA	NA	NA	NA	NA
Loforte *et al.* [40]	$PaCO_2$ mm Hg 63 ±20 PaO_2 mm Hg 68 ±39 PaO_2/FIO_2 78.7 ±39.3 PEEP (cm H_2O) 13.3 ±4.1	Lopinavir 53.5% Ritonavir 50.7% Remdesivir 22.5% Tocilizumab 29.6% Chloroquine 83.1%	NA	5.5 (1.6–7.1)	15 (8–23)	24 (14–37)/ 30 (18–45)

Table IV. Cont.

Study	Severity of illness parameters, mean	Treatments received (*n* %)	Days from symptom to mechanical ventilation	Days from intubation to cannulation	ECMO duration [days]	Days on ICU/ Hospital length of stay
Bergman *et al.* [41]	SOFA 7.10(02.1) pH 7.3 (00.12) PCO_2 56.5 (14.7) PaO_2 62.2 (15.9) P/F ratio 72.3 (22.7) PEEP cm H_2O 13.70	Remdesivir 67.4% IL-6 inhibitor 56.5% Steroids 45.7% Hydroxychloroquine – azithromycin 19.6% Convalescent plasma 47.8%	10 (8–13.75)	NA	22 (13–36)	33.(22–51)/ 39.5 (29–56)
Li *et al.* [42]	SOFA 9.0 ±3.1 APACHE II 12.4 ±3.8 pH 7.39 ±0.11 $PaCO_2$, mm Hg 56 ±20 PaO_2, mm Hg 66 ±19 PaO_2/FIO_2 ratio < 80 mm Hg for 6 h 74% PaO_2/FIO_2 ratio 76 ±29	Lopinavir/ritonavir 55% Arbidol 23% Oseltamivir 19% Ganciclovir 13% Ribavirin 7% Remdesivir/placebo 3%	19 (12–23.5)	2 (1–4)	14 (4.5–35)	NA
Biancari *et al.* [43]	SOFA score 10.1 (4.4) pH 7.23 (0.09) $PaCO_2$, mm Hg 61 (17) PaO_2/FIO_2 ratio, mm Hg 71 (23) PEEP, cm H_2O 12.4 (3.7)	Lopinavir/ritonavir 20.5% Oseltamivir 3.8% Ganciclovir 3.8% Acyclovir 3.8% Emtricitabine/tenofovir 0.8% Tocilizumab 6.8% Corticosteroids 35.6% Hydroxychloroquine/chloroquine 25% Convalescent plasma 4.5% Cytokine absorber 6.8%	30.5 (21.4)	5.8 (5.3)	14.6 (11.0)	NA/36.6 (28.1)
Mustafa *et al.* [44]	pH 7.25 (0.01) $PaCO_2$, mm Hg 68.2 (2.3) PaO_2, mm Hg 62.3 (1.9) PaO_2/FIO_2, mm Hg 65.0 (2.2) PEEP, cm H_2O 15.6 (0.4)	NA	4.9 ±0.5	3.9 (0.4)	38.5 (4.2)	NA/56.6 (4.2)
Ogura *et al.* [45]	PaO_2/FIO_2 86 (71–102) PEEP cm H_2O 12 (10–15)	NA	NA	3 (1–5)	NA	NA
Cho *et al.* [46]	NA	NA	2 (0–3)	NA	16 (8–25)	NA/30 (19–46)
Zaaqoq *et al.* [47]	SOFA 8 (5–10) PaCO2 49 (37–59) PaO_2/FIO_2 84 (61–126) PEEP cm H_2O 12 (10–16)	NA	NA	4 (2–6)	NA	NA/32 (20–47)
Suwalski *et al.* [48]	NA	NA	NA	7 (3–9)	18 (7.3)	NA

Table IV. Cont.

Study	Severity of illness parameters, mean	Treatments received (*n* %)	Days from symptom to mechanical ventilation	Days from intubation to cannulation	ECMO duration [days]	Days on ICU/ Hospital length of stay
Jacobs *et al.* [49]	P/F Ratio (SD) 69.5 (27.0)	Interleukin-6, Blocker 61.6% Steroids 28% Hydroxychloroquine 77% Convalescent plasma 47.6%	7.45 (6.82)	4.81 (4.72)	20.3 (16.1)	NA/20.3 (16.1)
Kunavarapu *et al.* [50]	SOFA 7.6 (2.8) SpO_2 (%) 87.9 (11.8)	Convalescent plasma 76.9%	NA	2.42 (2.6)	20.9 (21.7)	NA
Shaefi *et al.* [51]	pH – 7.30 (7.23–7.36) PaO_2/FIO_2 ratio, mm Hg – 85 (66–120) PEEP, cm H_2O – 15 (12–18) IMV – 78.4%	NA	NA	2 (0–5)	16 (10–23)	31 (20–43)/ 39 (28–53)
Bermea *et al.* [52]	NA	NA	NA	NA	NA	NA
Fröhlich *et al.* [53]	NA	NA	NA	NA	Time on ECMO was < 48 h 28.3% 2–12 days 47.2% 12–32 days 15.1%	NA
Luyt *et al.* [54]	SOFA 12 (10–14)	Lopinavir/ritonavir 18% Remdesivir 12% Hydroxychloroquine 40%	11 (7–14)	NA	21 (10–34)	48 (34–68)/NA
Zhang *et al.* [55]	SOFA score 7 (4–10) Murray ≥ 3 pH 7.30 (7.19–7.36) $PaCO_2$ mm Hg 67.5 (53.1–75.8) PaO_2/FIO_2 67.5 (58.9–77.8)	Remdesivir 13.8% Anakinra 24.1% Methylprednisolone 82.8% Hydrocortisone 3.4% Hydroxychloroquine 6.9%	NA	5 (2–6)	13 (8–20)	NA
Supady *et al.* [56]	SOFA 9.0 (8.0–10.0) pH 7.34 (7.17–7.39) $PaCO_2$, mm Hg 65.5 (42.5–80.1) PaO_2, mm Hg 57.3 (48.5–70.7) PaO_2/FIO_2, mm Hg 62.7 (48.5–72.7)	Remdesivir 29% Lopinavir–ritonavir 18% Tocilizumab 12% Methylprednisolone 53% Hydroxychloroquine 24%	5 (0.5–11)	NA	NA	NA
Lebreton *et al.* [57]	SOFA 12 (9–14) pH 7.31 (7.23–7.37) PaCO2, mm Hg 57 (48–67) PaO_2/FIO_2, mm Hg 61 (54–70) SaO2 88% (83–92)	Steroids 20%	NA	5 (3–7)	14 (8–26)	30 (17–47)/NA

SOFA – Sequential Organ Failure Assessment, APACHE II – Acute Physiology and Chronic Health Evaluation, IMV – invasive mechanical ventilation, FiO_2 – fractional inspired oxygen, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, PaO_2/FiO_2 – ratio of arterial oxygen partial pressure to fractional inspired oxygen, MAP – mean airway pressure, P_{IP} – peak inspiratory pressure, IV Ig – intravenous immunoglobulin, anti-IL – anti-interleukin.

et al. [25], Yang *et al.* [26], Raasveld *et al.* [27], Fang *et al.* [30], Garfield *et al.* [31], Supady *et al.* [34, 56], Schmidt *et al.* [36], Arachchillage *et al.* [37], Saeed *et al.* [38], Loforte *et al.* [40], Bergman *et al.* [41], Li *et al.* [42], Biancari *et al.* [43], Mustafa *et al.* [44], Ogura *et al.* [45], Zaaqoq *et al.* [47], Jacobs *et al.* [49], Shaefi *et al.* [51], Zhang *et al.* [55] and Lebreton *et al.* [57]. Of all these studies, 2 patients had ECMO initiated while receiving non-invasive mechanical ventilation (Yang *et al.*) [26], (Fang *et al.*) [30]. In Yang *et al.* [26] the patient was intubated 2 days later and ventilated invasively. In Fang *et al.* [30] the patient received ECMO therapy while awake and without mechanical ventilation. The ventilation parameters are summarized in Table IV.

Intervention/treatment

Regarding the pharmacological intervention, the antiviral remdesivir was used in 10 studies and varied between 3% (Li *et al.*) [42] and 67.4% (Bergman *et al.*) [41]. The monoclonal antibody (MAB) tocilizumab, has been used in 10 studies, ranging from 5.3% (Arachchillange *et al.*) [37] to 61.6% (Jacobs *et al.*) [49]. Steroid treatment was used in 11 studies from 20% (Lebreton *et al.*) [57] to 82.8% (Zhang *et al.*) [55]. The use of hydroxychloroquine/chloroquine was registered in 8 studies and ranged from 6.9% (Zhang *et al.*) [55] to 83.1% (Loforte *et al.*) [40]. The use of intravenous immunoglobulin has been reported in three studies, from 3% (Raasveld *et al.*) [27] to 56.8% (Fang *et al.*) [30]. Convalescent plasma/plasmapheresis was used in nine studies. The use of convalescent plasma ranges from 4.5% (Biancari *et al.*) [43] to 76.9% (Kunavarapu *et al.*) [50], while the use of plasmapheresis varies from 1% (Raasveld *et al.*) [27] to 9.2% (Arachchillage *et al.*) [37]. The use of a cytokine absorber has been reported in two studies, 6.8% in Biancari *et al.* [43], and 18% in Raasveld *et al.* [27], while stem cell treatment was used in only one study by 12.5% of patients [25] (Table IV).

Hospitalization time

The shortest length from symptom onset to invasive mechanical ventilation initiation was 2 days reported by Saeed *et al.* [38] and Cho *et al.* [46], while the longest duration was 30.5 days registered by Biancari *et al.* [43]. Between the onset of invasive mechanical ventilation and ECMO initiation, the shortest period was 1.5 days reported by Yang *et al.* [26], while the longest was 7 days reported by Suwalski *et al.* [48].

ECMO duration varied; the shortest time is described by Raasveld *et al.* [27], Fang *et al.* [30], Doyle *et al.* [35] and Zang *et al.* [55] with 13 days, and the longest period was reported by Mustafa *et al.* [44] with 38.5 days.

The shortest period of ICU and hospital lengths of stay was 24 days reported by Loforte *et al.* [40], and 20.3 days registered by Schmidt *et al.* [36], respectively, while the longest time spent was reported by Schmidt *et al.* [36] for both places, 50 days in the ICU and 74 days in hospital.

Adverse events related to ECMO usage

Acute kidney injury

Acute kidney injury requiring renal replacement therapy varied between 0% in Weir-McCall *et al.* [32] and 87% in Li *et al.* [42], as shown in Table V.

Acute pulmonary embolism and deep vein thrombosis

Fourteen studies reported venous and pulmonary thromboembolic events.

Schmidt *et al.* presented a 14% rate of pulmonary embolism [36] with a similar rate in Biancari *et al.*, of 13.6% [43]. Garfield *et al.* reported 69.8% rate of pulmonary embolism [31], Arachchillage *et al.* 66.2%, with 19.1% deep vein thrombosis [37]. Kunavarapu *et al.* observed that 15.4% of patients had deep vein thrombosis [50], with a similar rate in Saeed *et al.* [38] (15%). Also, similar rates of deep vein thrombosis were observed in Biancari *et al.* [43] (11.4%), and Raasveld *et al.* [27] with a 11% venous thrombotic event rate. Weir-McCall *et al.* reported 52% pulmonary artery thrombus with 8% venous thrombus [32], while Doyle *et al.* reported that 37% of all pulmonary arteries had filling defects, 53% of patients had deep vein thrombosis and 33.3% pulmonary embolism [35].

Lebreton *et al.* reported 17.5% thromboembolic complications [57], having similar rates with Shaefi *et al.*, 20% (18.4% with deep vein thrombosis, and 1.6% with pulmonary embolism) [51]. Bisell *et al.* reported a 3.1% rate of deep vein thrombosis and 3.1% rate of pulmonary embolism [33]. Shaefi *et al.* [51], Loforte *et al.* [40], and Zhang *et al.* [55] reported pulmonary embolism rates ranging from 1.6% to 27.9% while Loforte *et al.* [40] and Zhang *et al.* [55] revealed deep vein thrombosis rates between 2.8% and 39.5%.

Acute coronary syndromes

None of the included studies reported acute coronary syndromes.

Pneumothorax

Pneumothorax was diagnosed in 8 studies and varied between 7.6% (Lebreton *et al.*) [57] and 47.5% (Tabatai *et al.*) [25]. Kunavarapu *et al.* reported 1 case of hemopneumothorax [50].

Table V. Adverse events related to ECMO usage

Study	Median age	Acute renal failure	Deep vein thrombosis/Pulmonary embolism	Myocardial infarction	Pneumothorax	Sepsis	Stroke/Intracranial haemorrhage
Tabatabai *et al.* [25]	43.2 (8.9)	NA	NA	NA	47.5%	17.5% Urinary tract infection 72.5% Bacteraemia 55% Pneumonia	6.7% intracranial haemorrhage-cause of death
Yang *et al.* [26]	62 (33–78)	71.2%	NA	NA	13.7%	57.5%	4.1% intracranial haemorrhage associated with gastro-intestinal haemorrhage 2.7% only cerebral haemorrhage
Raasveld *et al.* [27]	52 (47–57)	55%	11% venous thrombotic event/3% PE	NA	NA	56% infections: 23 ventilator-associated pneumonia, 9 catheter-related bloodstream infection, 6 superinfection	1.5% ischaemic strokes/10% haemorrhagic stroke
Nguyen *et al.* [28]	NA	NA	NA	NA	NA	NA	NA
Shih *et al.* [29]	50 (41–56)	NA	NA	NA	NA	20% bacterial pneumonia infection	0% strokes, 9.4% haemorrhagic brain injury
Fang *et al.* [30]	58.5 (47–66.5)	67.4%	NA	NA	10.2%	79.6% nosocomial infection	4.5% cerebral haemorrhage
Garfield *et al.* [31]	46 (7.8)	45.3%	69.8% PE	NA	16.9%	NA	11.3% ischaemic strokes, 20.8% intracranial haemorrhage
Weir-McCall *et al.* [32]	45.0 ±9.4	0	52%-pulmonary artery thrombus, 8% venous thrombus	NA	NA	NA	5% brain ischaemia, 14% intracranial haemorrhage
Bissell *et al.* [33]	51 (14)	NA	3.1% DVT, 3.1% PE	NA	NA	NA	NA
Supady *et al.* [34]	59 (53–66)	NA	NA	NA	NA	NA	NA
Doyle *et al.* [35]	46.1 (35.6–53.2)	NA	53% DVT/ 37% – all pulmonary artery filling defects, 33.3% PE, 5% pulmonary immunothrombosis	NA	NA	NA	3.9% ischaemic strokes, 16% intracranial haemorrhage-7 subarachnoid, 1 subdural
Schmidt *et al.* [36]	51 (43–58)	(40%)	14% PE	NA	(11%)	NA	6.2% – 2 ischaemic, 8 haemorrhagic
Arachchillage *et al.* [37]	47 (23–65)	NA	19.1% DVT/66.2% PE, 14.7% DVT + PE	NA	NA	NA	3.9% ischaemic strokes/34% ICH

Table V. Cont.

Study	Median age	Acute renal failure	Deep vein thrombosis/Pulmonary embolism	Myocardial infarction	Pneumothorax	Sepsis	Stroke/Intracranial haemorrhage
Saeed *et al.* [38]	49 (39–57)	46%	15% DVT	NA	NA	153 (55%): 91 bacterial pneumonia, 92 bacteraemia, 8 central line infection, 31 urinary infection	1% ischaemic strokes, 6% haemorrhagic strokes
Onorati *et al.* [39]	NA	NA	NA	NA	NA	NA	NA
Loforte *et al.* [40]	55.4 (46.1–64.7)	4.2%	2.8% DVT, 5.6% PE	NA	NA	19.7%	8.5% ischaemic strokes
Bergman *et al.* [41]	51.3 (10)	45.7%	NA	NA	NA	1.3%	NA
Li *et al.* [42]	58 (46–64.5)	87%	NA	NA	NA	45% septic shock, 97% nosocomial infection	3% intracerebral haemorrhage
Biancari *et al.* [43]	51.1 (41.4–60.8)	64.1%	11.4% DVT, 13.6% PE	NA	NA	31.8% bloodstream infection	14.4% ischemic strokes
Mustafa *et al.* [44]	49 (22–67)	22.5%	NA	NA	NA	17.5% septic shock, 23.8% VAP	8.8% strokes
Ogura *et al.* [45]	60 (53–68)	NA	NA	NA	NA	NA	NA
Cho *et al.* [46]	52 (12.0)	NA	NA	NA	NA	NA	7.8% – 5.3% haemorrhagic stroke, 1.1% ischaemic stroke, 1.4% unsuspected type
Zaaqoq *et al.* [47]	53 (43–60)	NA	NA	NA	NA	NA	NA
Suwalski *et al.* [48]	50.2 (8.9)	NA	NA	NA	NA	NA	NA
Jacobs *et al.* [49]	51 (40–59)	12/110 who died	NA	NA	1/110 who died	7/110 who died	5/110 who died had cerebral bleeding
Kunavarapu *et al.* [50]	47.8 (12.1)	NA	15.4% DVT	NA	1.9% – hemoptx	NA	3.9% strokes
Shaefi *et al.* [51]	49 (41–58)	21.8%	18.4% DVT/1.6% PE	NA	12.6%	34.7% Bacterial pneumonia, 18.4% Other culture documented infections	1.6% ischaemic stroke, 4.2% Intracranial haemorrhage
Bermea *et al.* [52]	NA	NA	NA	NA	NA	NA	33.3% intracranial haemorrhage
Fröhlich *et al.* [53]	57 (50–67)	NA	NA	NA	NA	NA	NA
Luyt *et al.* [54]	48 (42–56)	NA	NA	NA	NA	86% VAP	NA

Table V. Cont.

Study	Median age	Acute renal failure	Deep vein thrombosis/Pulmonary embolism	Myocardial infarction	Pneumothorax	Sepsis	Stroke/Intracranial haemorrhage
Zhang *et al.* [55]	46 (35.5–52.5)	44.2%	39.5% DVT, 27.9% PE	NA	11.6%	34.9% infection	7% ischaemic stroke, 16.3% Intracranial haemorrhage
Supady *et al.* [56]	60.5 (43.5–71.5)	NA	NA	NA	NA	29% died of septic shock in cytosorb group and 12% in the group without	12% intracranial haemorrhage
Lebreton *et al.* [57]	52 (45–58)	43%	17.5%	NA	7.6%	16%	11%

Infectious complications

18 studies described infectious complication rates ranging from 1.3 % in Bergman *et al.* [41] to 97% in Li *et al.* [42]. The most common infectious complications are nosocomial infections reported in Li *et al.* (97%) [42], and Fang *et al.* (79.6%) [30], followed by bacterial pneumonia reported by Tabatai *et al.* (55%) [25], Shaefi *et al.* (34.7%) [51], Shih *et al.* (20%) [29], and Saeed *et al.* [38], who reported 91/153 patients with bacterial pneumonia. Also, ventilator-associated pneumonia (VAP) was seen in 3 studies, Mustafa *et al.* [44] reporting 23.8%, Luyt *et al.* [54] 86% and Raasveld *et al.* [27] 23 of 40 patients with infectious complications. Sepsis was found in 1.3% of patients by Bergman *et al.* [41], 16% of patients by Lebreton *et al.* [57], 19.7% by Loforte *et al.* [40].

Yang *et al.* [26] found sepsis in 57.5% of patients, while septic shock was found in 17.5% of patients by Mustafa *et al.* [44], 45% of patients by Li *et al.* [42], and in 41% of cases in Supady *et al.* [56].

Other encountered complications were urinary infection [25, 38], bacteraemia [25, 38], and central line infections [27, 38].

Neurological impairments

Cerebral complications were mentioned in 25 studies, from no cerebrovascular accidents in Shih *et al.* [29] to 34% intracranial haemorrhage in Arachchillage *et al.* [37]. Cho *et al.* reported that cumulative probabilities for haemorrhagic and ischaemic stroke were higher at 90 days of ECMO support comparing to non-ECMO-supported cases [46]. The main complications of ECMO usage are presented in Table V.

Thrombosis and bleeding

Eight studies encountered acute ECMO circuit thrombosis with the highest rate in Zhang *et al.* [55] (39.5%). 3.8% of patients in Shih *et al.* [29], 6.1% in Bisell *et al.* [33], 9.9% in Arachchillage *et al.* [37], 10% in Lebreton *et al.* [57], 11% in Schmidt *et al.* [36], and 13% in Li *et al.* [42] had the same complication, with the lowest rate in Raasveld *et al.* [27] (1.5% cannula thrombosis and no pump thrombosis).

Mustafa *et al.* [44] reported the smallest rate of bleeding at insertion site, 1.3% of patients, with the highest rate reported by Yang *et al.* (32.9%) [26], with intermediate values in Shih *et al.* [29], Kunavarapu *et al.* [50], Fang *et al.* [30], Schmidt *et al.* [36], and Raasveld *et al.* [27]. Arachchillage *et al.* [37] and Tabatabai *et al.* [25] had the same rate of bleeding at insertion site, 15%.

Twenty-five studies [25–27, 29–38, 40–44, 46, 49–52, 55, 57] reported major bleeding with the necessity of blood transfusions in some cases

and they varied from 4.2% in Loforte *et al*. [40] to 92.1% in Arachchillage *et al*. [37]. The complications are presented in detail in Table VI.

Study quality

Quality score of the included studies ranged from 6 to 9, with a mean quality score of 7.42. This corresponds to a medium-to-high quality of the included studies. The detailed scores are provided in Table VII.

Discussion

Our systematic review included 33 articles from 10 countries with a total of 4 760 patients receiving ECMO for COVID-19 and we identified the benefits and the side effects of using ECMO in the COVID-19 patients with acute respiratory distress syndrome (ARDS) refractory to conventional management (Figure 2).

Reported mortality in our analysis is similar to the ECMO usage in non-COVID-19 ARDS, but with higher rates of bleeding and thrombotic complications. The need for anticoagulation on ECMO creates a higher bleeding risk profile that can be fatal in some cases, adding major bleeding that may require blood transfusions. Also, the high thrombotic status of SARS-CoV-2 infection sometimes creates the urgency of changing the entire ECMO circuit. In our opinion, acute kidney failure, major bleeding, and strokes are not only related to the usage of ECMO but also to the COVID-19 infection.

It is well known that the thrombogenic status in COVID-19 creates the premises of developing pulmonary thromboembolism, acute myocardial infarction, or strokes. In a systematic review that included patients with COVID-19, 39% had limb thrombosis, while 24% had cerebral and 9% had coronary events [58].

Other studies have reported a relation between acute coronary syndromes and COVID-19 caused by coronary artery thrombosis, even without a pre-existing atherosclerotic lesion [59, 60]. None of the studies included in our analysis reported acute coronary syndromes, but several reported pulmonary embolisms.

There are still gaps in establishing the key role that mechanical circulatory support may have in cardiogenic shock due to myocardial infarction in patients with COVID-19, but the high mortality rates in these patients may justify the usage of any circulatory support to improve patient's survival [61]. In a systematic review that analysed the impact of ECMO in COVID-19 patients the authors proposed a decision-making algorithm, by choosing the V-A ECMO in case of cardiogenic shock and V-V ECMO for patients without it [62].

Also, COVID-19 patient evolution may be influenced by the occurrence of the cytokine storm, which may require the addition of cytokine filters [63] to mechanical circulatory support, beside standard care therapy with cytokine receptor antagonists [64]. However, the results of a recently published randomised controlled study comparing ECMO with or without cytokine adsorption during the first 72 h of V-V ECMO for severe COVID-19 showed no benefits in terms of IL-6 reduction levels or survival of the patients but was associated with higher mortality in the cytokine adsorption group [56].

The use of ECMO appears to be an effective intervention and to bring improvements in selected patients with COVID-19-related ARDS as stipulated in the latest systematic reviews [65, 66]. These studies focused more on the efficacy of the V-V ECMO type and suggested clinical advice in the current era and ongoing pandemic.

In another systematic review [67] which included 18 studies that also analysed the effect of ECMO on improving COVID-19 patients' outcomes, the authors concluded with the need for future research.

The recently published ELSO guideline on ECMO in COVID-19 emphasizes the need of careful selection of the COVID-19 patients who might benefit from ECMO treatment, according to the patient's clinical profile but also to the medical system capacity, the recommendation for initiating ECMO being different if the capacity is conventional, expanded, near saturation or overwhelmed. The guideline clearly states that the mortality of the patients with severe COVID-19 treated by ECMO is similar to historical ECMO treated patients with ARDS of other causes [68].

In conclusion, our study has its limitations and strengths. There is a lack of ECMO standardization in COVID-19. We referred to ECMO in COVID, in general, because we did not have enough evidence to suggest what type of ECMO (V-V or V-A) has a more beneficial use.

We believe that ECMO may be a useful support device and rescue therapy in sustaining pulmonary function by using veno-venous type and for cardiac involvement, veno-arterial type ECMO usage may provide substantial benefits, but further studies need to be done.

The unknown mechanisms and effects of SARS-CoV-2 infection are still creating great pressure on medical systems worldwide. As studies described, the most severe cases require aggressive therapy, but sometimes standard care measures reach their limits.

The use of ECMO therapy in treating severe COVID-19 patients can be performed in a more standardised manner than at the beginning of the pandemic period, due to the recently published

Table VI. Thrombosis and bleeding complications on ECMO usage

Study	Pump/cannula thrombosis	Bleeding at site of insertion	Major bleeding
Tabatabai *et al.* [25]	NA	15%	67.5%
Yang *et al.* [26]	NA	32.9%	42.5% – 25 gastrointestinal haemorrhage, 6 respiratory tract haemorrhages
Raasveld *et al.* [27]	0%/1.5%	14%	54%
Nguyen *et al.* [28]	NA	NA	NA
Shih *et al.* [29]	3.8% complications of ECMO circuit	1.9%	37.7%
Fang *et al.* [30]	NA	4.5%	28.4% – –2 pulmonary haemorrhage, 19 gastrointestinal haemorrhage, 4 intracranial haemorrhage 9.2% died of lethal haemorrhage
Garfield *et al.* [31]	NA	NA	NA 20.8% intracranial haemorrhage
Weir-McCall *et al.* [32]	NA	NA	16% – 9 brain, 1 abdomen
Bissell *et al.* [33]	6.1%	NA	12.1%
Supady *et al.* [34]	NA	NA	NA
Doyle *et al.* [35]	NA	NA	11.7% major bleeding – 3 intracerebral, 2 retroperitoneal, 1 pleural
Schmidt *et al.* [36]	11%	10%	44%
Arachchillage *et al.* [37]	9.9%	15%	30.9%: intracranial haemorrhage – 34%, pulmonary haemorrhage – 26%, gastrointestinal haemorrhage – 11%, other sites – 23% A total of 92.1% received one or more red cell unit
Saeed *et al.* [38]	NA	NA	74% bleeding requiring transfusion 3% died of haemorrhagic shock
Onorati *et al.* [39]	NA	NA	NA
Loforte *et al.* [40]	NA	NA	4.2%
Bergman *et al.* [41]	NA	NA	23.9 number of transfusions
Li *et al.* [42]	13% oxygenator thrombosis	NA	35.4%
Biancari *et al.* [43]	NA	NA	79.5% RBC transfusion
Mustafa *et al.* [44]	NA	1.3%	12.5%
Ogura *et al.* [45]	NA	NA	NA
Cho *et al.* [46]	NA	NA	5.3% haemorrhagic stroke
Zaaqoq *et al.* [47]	NA	NA	NA
Suwalski *et al.* [48]	NA	NA	NA
Jacobs *et al.* [49]	NA	NA	NA 5/110 who died had cerebral bleeding
Kunavarapu *et al.* [50]	NA	3.8%	32.7%
Shaefi *et al.* [51]	NA	NA	27.9% systemic bleeding events
Bermea *et al.* [52]	NA	NA	33.3% intracranial haemorrhage
Fröhlich *et al.* [53]	NA	NA	NA
Luyt *et al.* [54]	NA	NA	NA
Zhang *et al.* [55]	39.5%	NA	18.6%
Supady *et al.* [56]	NA	NA	12% intracranial haemorrhage in both groups 18% died of pulmonary haemorrhage
Lebreton *et al.* [57]	10%	NA	38% – major bleeding 9% – intracranial haemorrhage

Table VII. Newcastle-Ottawa scale for assessment of quality of included studies (each asterisk represents that individual criterion within the subsection was fulfilled)

Quality assessment Criteria	(1) Representativeness of the exposed cohort	(2) Selection of the nonexposed cohort	(3) Ascertainment of exposure	(4) Demonstration that outcome of interest was not present at the start of the study	(5) Adequate control for the most important confounder?	(6) Adequate control for any additional factor?	(7) Assessment of outcome	(8) Was follow-up long enough for outcomes to occur?	(9) Adequacy of follow-up of cohorts	Overall quality score (maximum = 9)
Acceptable (*)	Representative of average adult in community (age/sex/being at risk of disease)	Drawn from the same community as the exposed cohort	Secure record, structured interview				Independent or blind assessment		Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	
Tabatabai *et al.* [25]	*	–	*	*	*	–	*	*	–	6
Yang *et al.* [26]	*	–	*	*	*	*	*	*	–	7
Raasveld *et al.* [27]	*	–	*	*	*	*	*	*	*	8
Nguyen *et al.* [28]	*	*	*	*	*	*	*	–	*	8
Shih *et al.* [29]	*	–	*	*	*	*	*	*	*	8
Fang *et al.* [30]	*	*	*	*	*	*	*	*	*	9
Garfield *et al.* [31]	*	–	*	*	*	–	*	*	*	7
Weir–McCall *et al.* [32]	*	–	*	*	*	*	*	–	–	6
Bissell *et al.* [33]	*	–	*	*	–	–	*	*	*	6
Supady *et al.* [34]	*	–	*	*	*	*	*	*	*	8
Doyle *et al.* [35]	*	–	*	*	*	*	*	*	*	8
Schmidt *et al.* [36]	*	–	*	*	*	*	*	*	*	8
Arachchillage *et al.* [37]	*	–	*	*	*	*	*	*	*	8
Saeed *et al.* [38]	*	–	*	*	*	–	*	*	–	6
Onorati *et al.* [39]	*	–	*	*	*	*	*	–	–	6
Loforte *et al.* [40]	*	–	*	*	*	*	*	*	*	8
Bergman *et al.* [41]	*	–	*	*	*	*	*	*	*	8

Table VII. Cont.

Quality assessment Criteria	(1) Representativeness of the exposed cohort	(2) Selection of the nonexposed cohort	(3) Ascertainment of exposure	(4) Demonstration that outcome of interest was not present at the start of the study	(5) Adequate control for the most important confounder?	(6) Adequate control for any additional factor?	(7) Assessment of outcome	(8) Was follow-up long enough for outcomes to occur?	(9) Adequacy of follow-up of cohorts	Overall quality score (maximum = 9)
Acceptable (*)	Representative of average adult in community (age/sex/being at risk of disease)	Drawn from the same community as the exposed cohort	Secure record, structured interview				Independent or blind assessment		Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	
Li *et al.* [42]	*	–	*	*	*	*	*	*	*	8
Biancari *et al.* [43]	*	–	*	*	*	*	*	*	*	8
Mustafa *et al.* [44]	*	*	*	*	*	*	*	*	*	9
Ogura *et al.* [45]	*	–	*	*	*	–	*	–	*	6
Cho *et al.* [46]	*	*	*	*	*	*	*	*	*	9
Zaaqoq *et al.* [47]	*	–	*	*	*	–	*	–	*	6
Suwalski *et al.* [48]	*	–	*	*	–	–	*	*	*	6
Jacobs *et al.* [49]	*	–	*	*	*	–	*	*	*	7
Kunavarapu *et al.* [50]	*	–	*	*	*	–	*	*	*	7
Shaefi *et al.* [51]	*	*	*	*	*	*	*	*	*	9
Bermea *et al.* [52]	*	–	*	*	*	*	*	–	*	7
Fröhlich *et al.* [53]	*	–	*	*	*	–	*	*	–	6
Luyt *et al.* [54]	*	–	*	*	*	*	*	*	*	8
Zhang *et al.* [55]	*	–	*	*	*	*	*	*	*	8
Supady *et al.* [56]	*	–	*	*	*	*	*	*	*	8
Lebreton *et al.* [57]	*	–	*	*	*	*	*	*	*	8

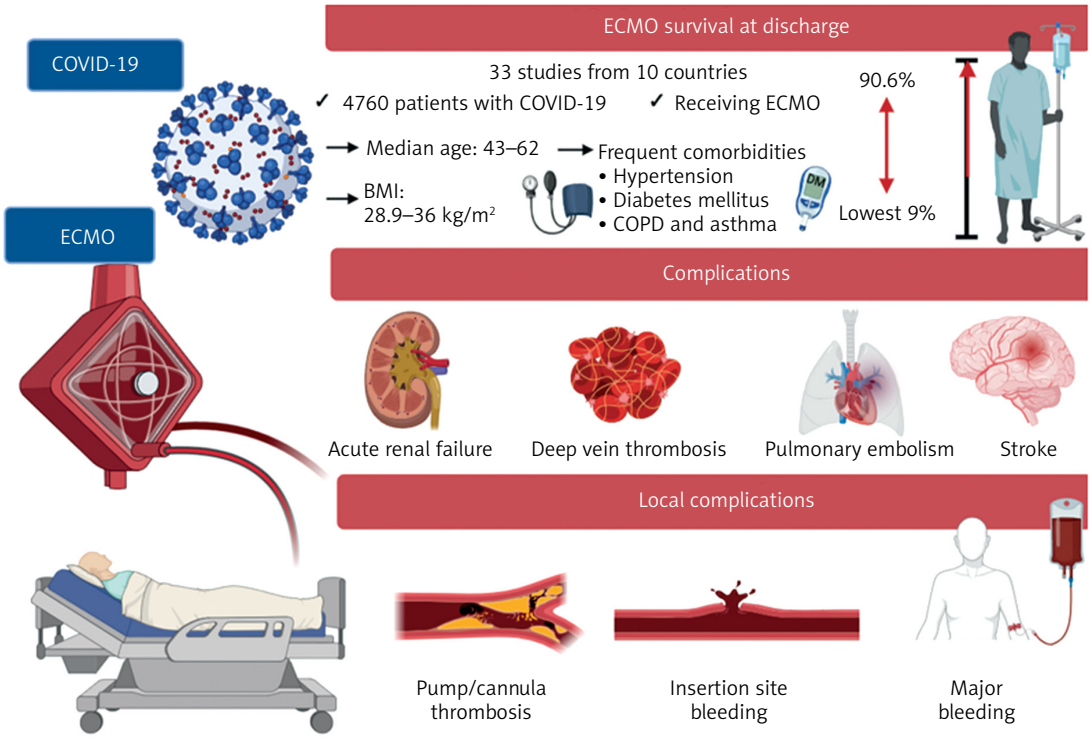

Figure 2. Overview of ECMO usage

study results. However, patients' clinical status and prognosis and the medical system capacity must be taken into account when deciding to start ECMO on a COVID-19 patient, since this treatment does not always save lives.

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Conflict of interest

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