Use of Extracorporeal Membrane Oxygenation (ECMO) for patients with Acute Respiratory Distress Syndrome (ARDS) in COVID-19

Rapid Review

Prepared by:
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Service Line	Rapid Review
Version	1
Publication date	10 September 2020
Report Length	66 pages

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1. CONTEXT AND POLICY ISSUES

In early 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing novel coronavirus disease 2019 (COVID-19). This is a global pandemic affecting more than 213 countries and regions with at least 26,763,217 cases and 876,616 deaths worldwide as of 6 September 2020 (World Health Organization, 2020a).

As of September 6, 2020, there are a total of 237, 365 COVID-19 cases in the Philippines (48,803 active cases, 184,687 recoveries, 3,875 deaths), 683 (1.4%) of which are severe cases, and 976 (2%) are critical cases (DOH, 2020). Similar to previous outbreaks of influenza, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), COVID-19 shares similar clinical characteristics throughout the disease course (Jiang et al., 2020). The spectrum of clinical characteristics of COVID-19 varies from asymptomatic and symptomatic patients which may range from mild flu-like symptoms, moderate to severe pneumonia, and acute respiratory distress syndrome (ARDS) to extrapulmonary manifestations and systemic complications such as organ failure, sepsis and septic shock (Tu, Tu, Gao, Shao, & Sheng, 2020).

COVID-19 damages the lungs because of the propensity of the receptor-binding domain of the S protein of the SARS-CoV-2 to bind to the human receptor Angiotensin-converting enzyme 2 (ACE2). The ACE2 receptor is particularly seen in the lungs, heart, kidney, and the gastrointestinal tract. Researchers propose that the large surface area and the concentration of ACE2 receptors in the lungs are associated with the pulmonary manifestations of COVID-19 (Wan, Shang, Graham, Baric, & Li, 2020).

To date, a definitive cure remains unknown but clinical trials were started through the Solidarity clinical trials which have enrolled patients in 21 countries as of July 1, 2020. The inter-country trials aim to identify an effective treatment for COVID-19 (World Health Organization, 2020b). Even though the search for a cure is ongoing, multiple supportive therapies have been recommended such as conservative fluid management, administration of empiric antimicrobials, corticosteroids, supplementary oxygen therapy, and non-invasive and/or invasive mechanical ventilation based on the treatment guideline for COVID-19 developed by the Philippine Society for Microbiology and Infectious Diseases. It also states that if invasive mechanical ventilation fails to provide adequate oxygenation and ventilation, then extracorporeal membrane oxygenation (ECMO) is recommended (PSMID, July 2020).

The ECMO is a machine that supplements the function of the heart and lungs when there is either respiratory or cardiac failure. The machine sends blood from the patient to an oxygenator component of the ECMO machine, then returns it to the patient for circulation. It is combined with invasive mechanical ventilation as part of a lung protective strategy (ATC, 2020). There are two types of ECMO - Veno-arterial (VA) and Veno-venous (VV). These two types are differentiated by the route of the blood flow. The VA ECMO completely bypasses the heart by collecting blood from the right atrium, oxygenates it in the machine, then returns the blood through the aorta. This type is mainly for patients who have a combined heart and lung dysfunction. Meanwhile, the VV type collects and returns the blood at the right atrium via a double lumen catheter. The VV type is mainly for patients who have respiratory failure but with a functioning heart. (ELSO, 2020). Since its early introduction in the 1970s and continuous development through the years, it has been used for several diseases with similar respiratory manifestations including the previous viral outbreaks such as SARS and MERS. However, the evidence on its overall benefit remains to be inconclusive, to date. Its previous use for SARS and MERS did not show conclusive evidence in reducing mortality. The lack of randomized controlled trials or adequately case-matched cohort studies impeded formation of a definitive recommendation

regarding the use of ECMO during cases of ARDS secondary to infections (Cho et. Al, 2020) As of September 7, 2020, the Extracorporeal Life Support Organization (ELSO) reports a total of 2,437 COVID-19 patients who have used ECMO, with a 54% rate (970/ 1787) of being discharged alive after using ECMO. The patient characteristics, severity of ARDS, length of using ECMO, and the length of hospitalization was not described in the website (ELSO, 2020).

In light of a proposal for the Philippine Health Insurance Corporation (PhilHealth) to cover ECMO for COVID-19, this rapid review was undertaken to review the current use of ECMO in COVID-19 by the Philippines and other countries, its safety and effectiveness for COVID-19 patients with ARDS, and the potential resource implications of its implementation.

2. POLICY AND RESEARCH QUESTIONS

POLICY QUESTION

Should ECMO for COVID-19 patients with acute respiratory distress syndrome (ARDS) be recommended for use and covered by PhilHealth?

RESEARCH QUESTIONS

1. **Treatment guidelines and evidence synthesis on the use of ECMO**

   1.1 Which country/countries have implemented ECMO for the management of ARDS secondary to COVID-19 infection?

   1.2. What is the current position/ recommendation of HTA agencies regarding the use of ECMO for the management of ARDS secondary to COVID-19 infection?

2. **Clinical efficacy / effectiveness and safety**

   Among critically ill COVID-19 patients with acute respiratory distress syndrome, is ECMO alone or combined with mechanical ventilation compared to mechanical ventilation alone effective and safe in improving the survival rate, decreasing the hospitalization days, resolving the symptoms and decreasing the incidence of adverse events?

3. **Resource requirements**

   What are the technical, infrastructure, logistical and organizational needs in implementing ECMO for COVID-19 patients with ARDS?

3. KEY FINDINGS

In determining the safety and effectiveness of the use of ECMO in COVID-19 patients with acute respiratory distress syndrome, this rapid review aimed to capture and present currently existing treatment guidelines and HTA review recommendations from selected countries. This review also intended to synthesize the most recent information on the efficacy and effectiveness of ECMO in both COVID-19 and non-COVID-19 patients.

GUIDELINE RECOMMENDATIONS Of the 15 COVID-19 treatment guidelines reviewed, nine guidelines (WHO, Philippines, Australia, Canada, China, Indonesia, Japan, United Kingdom- National Health Service, and United Stated- National Institutes of Health) mentioned the use of ECMO. Among these guidelines, WHO, Australia, Canada, and the US-NIH only issued a moderate or conditional recommendation for the use of ECMO in patients with COVID-19 in ARDS due to lack of high-quality evidence supporting ECMO. In general, these guidelines recommend reserving the use of ECMO once the lung protective ventilation strategy via mechanical ventilation has failed to achieve adequate

oxygenation and ventilation. Based on their assessment, ECMO can be used to manage severe acute respiratory failure as advised by intensive care clinicians when conventional intensive care management has failed. On the other hand, the five countries (from Philippines, China, Indonesia, Japan, and the United Kingdom) did not specify the strength of their recommendation.

HTA REVIEW RECOMMENDATIONS Of the 11 HTA agencies reviewed, UK-NICE is the only HTA agency which was able to publish a rapid guideline that covered ECMO which mainly specified the treatment for adult COVID-19 patients needing critical care. The review includes details on the admission to hospital/ critical care, clinical decision making, and critical care referral algorithm. No economic evaluation was performed in the creation of this rapid guideline mainly due to time constraints.

EVIDENCE ON CLINICAL EFFICACY/ EFFECTIVENESS AND SAFETY A total of three completed studies and eight future or on-going studies were included in this review. Two of the three completed studies are systematic reviews (SRs) (Haiduc, Alom, Melamed & Harky, 2020; Aretha, Fligou, Kiekkas, Karamouzos & Voyagis, 2019), and one is a case series report (Mustafa, Alexander, Joshi, Tabachnick, Cross, Pappas & Tatooles, 2020). Haiduc, et al. and Mustafa, et al. included studies on COVID-19 patients while Aretha, et al. focused on non-COVID-19 patients.

Completed studies on ECMO

All three completed studies focused ECMO as an intervention, with the SR by Aretha et al. (2019) also including extracorporeal carbon dioxide removal ($ECCO_2R$) in the scope of their study. Haiduc et al. (2020) did not indicate the comparator in their included studies, while Mustafa et al. (2020) did not have a comparator group as it is a case series report. Studies included in Aretha et al. compared ECMO or $ECCO_2R$ with either no ECMO or mechanical ventilation. Due to the difference in population, implementation of the intervention (i.e. eligibility of patients to ECMO and/or different timing of ECMO initiation), and study designs of the studies included, pooling of outcomes was not performed.

Below are the key findings on the clinical efficacy/effectiveness and safety of ECMO based on the completed studies included in this rapid review:

- **Survival**
  - Evidence among COVID-19 patients: The reported mortality of patients who used ECMO was 19.83% (95/479), as reported by the SR of Haiduc et al., combining the result of 25 observational studies (n=3428). This review, however, did not report the mortality of its comparator group. Meanwhile, the case series by Mustafa et al. among COVID-19 patients who received ECMO observed a relatively lower overall mortality rate among patients who used ECMO reported at 15% (6/40). As there is no control group in Mustafa et al. (2020) and no outcomes reported for the control group in Haiduc et al., the relative treatment effect of ECMO in terms of decreasing mortality cannot be established.
  - Evidence among non-COVID-19 patients: The use of ECMO was suggestive of harm in the increase of the mortality rates, but was not statistically significant. [OR 2.23, 95%CI: (0.18, 28.07)] based on a meta-analysis performed by Aretha et al. which included two RCTs.
- **Hospitalization days**
  - Only Mustafa et al. reported the mean duration of hospitalization among COVID-19 patients who used ECMO which was observed to be at 44.5 days [95% CI (40.37, 48.63), n=29]. As this is a case series, the study had no comparator group; hence, the relative treatment effect of ECMO in terms of decreasing hospitalization days cannot be established.

- **Duration of ECMO treatment**
  - Only Mustafa et al. reported the mean duration of ECMO treatment (i.e., the time it takes from initiation of ECMO to ECMO decannulation), which was 29.9 days [95% CI: (24.4-35.9 days), n=32]. Individual patient outcomes were not reported.
- **Resolution of symptoms**
  - None of the included studies in this review evaluated the effect of ECMO on resolving symptoms.
- **Incidence of adverse events**
  - Evidence among COVID-19 patients: no reports from the studies of Haiduc et al. and Mustafa et al.
  - Evidence among non-COVID-19 patients: The meta-analysis of Aretha et al. showed that there was significant increase in the risk of bleeding episodes when using ECMO by almost 3 times more [OR: 2.93, 95% CI (1.84, 4.68)]; (two RCTs, two quasi-RCTs, two observational studies).
  - The risk of barotrauma/ pneumothorax was towards an increase in the odds but this was not significant among patients who used ECMO [OR: 2.38, 95% CI (0.84, 6.75)] (two RCTs, two quasi-RCTs, two observational studies). The results were based on pooling mixed study designs. A study which evaluated a different intervention ($ECCO_2R$) was also included in the pooling for this outcome.
- **Risk of bias assessment**: In terms of the risk of bias assessment of the two SRs, Haiduc, et al. did not report the individual RoB of its included studies. On the other hand, the RoB of the primary studies included in Aretha, et al. were highly varied. Their included clinical trials, either randomized or non-randomized were rated by the authors as low risk of bias (n=7), while their included observational studies were rated to be of high risk of bias (n=8), which might be due to the unsuitable risk of bias tool applied. However, we find the rating of low ROB as questionable since the study designs are non-randomized, hence, have inherent high ROB.

  Based on our critical appraisal of the three completed studies, the two systematic reviews were of critically low quality. Meanwhile, the case series report was rated with low internal validity and applicability.

Ongoing and future studies on ECMO

As for the on-going trials on ECMO, there are eight ongoing studies on clinicaltrials.gov that seeks to expand the evidence on the use of ECMO in COVID-19 patients with ARDS. Out of the eight, only one NCT04343404 has been completed but the results and manuscript of the said study is not available.

RESOURCE REQUIREMENTS There are eight hospitals with ECMO machines nationwide. Of these eight hospitals, four are public and four are private hospitals. Overall, there are only 13 ECMO machines in the country, 12 of which are in Metro Manila and one in Davao City. The use of ECMO would need a fully equipped intensive care unit (ICU), with negative pressure ventilation if used for a COVID-19 patient. A patient would need at least five specialist doctors and four allied health staff per shift (three shifts per day). There is a daily need for multiple units of different blood products.

Based on previous hospitalization data on non-COVID-19 patients from NKTI in June 2018 to March 2020 (n=21), the use of ECMO would need an average of Php 4,082,472.68 for an average of 11-day ECMO use per patient, based on the submitted information from NKTI. Additionally, the acquisition

cost of each ECMO machine is around Php 8 to 10 million based on Department of Health -Health Facilities Development Bureau (DOH-HFDB) data.

4. METHODOLOGY

4.1. Literature Search Methods

Through targeted search, two reviewers searched for national treatment guidelines on the use of ECMO for COVID-19 from 14 international organizations and countries. Additionally, search as conducted to identify HTA agency reports, recommendations and/or positions on the use of ECMO for COVID-19.

Treatment guidelines	15 treatment guidelines from the World Health Organization (WHO), European Union (EU), Australia, Canada, China, Indonesia, Japan Malaysia, Philippines, Singapore, South Korea, Thailand, United Kingdom, United States of America, and Vietnam
Reviews from HTA agencies	11 HTA agencies from Australia, Canada, China, Indonesia, Malaysia, Singapore, South Korea, Thailand, United Kingdom, United States of America, and Vietnam

There were no language restrictions in the targeted search for guidelines and HTA reports. Google translate was used for direct English translation of non- English contents in the websites and issuances (i.e. Indonesia). Only official country websites were included. For treatment guidelines and HTA reports, the last search was conducted on August 13, 2020.

For the review of the efficacy or effectiveness of ECMO, systematic search of relevant studies on clinical efficacy or effectiveness was conducted by two reviewers (MSF and PJE) through PubMed by using combinations of relevant search terms detailed in Appendix A. The last search was conducted on August 7, 2020. There were no language restrictions in the systematic search. Google translate was intended to be used if a non-English study is included.

Additionally, the authors searched clinicaltrials.gov for relevant clinical trials using the keywords: “ECMO” and “COVID-19”

4.2. Selection Criteria and Methods

Five review authors independently screened all titles and abstracts which were identified in the systematic search. The full text of potentially eligible studies based on relevance of their titles and abstract to the research question were accessed and independently screened against a set inclusion and exclusion criteria (Table 1). Note that despite the policy and research questions being specific to ARDS secondary to COVID-19 infection, an open search in terms of population was conducted to include evidence on ARDS due to other etiologies anticipating that there might be limited studies specifically on COVID-19. Any disagreement between review author was resolved through consensus.

All excluded studies which were read in full-text were recorded, noting their reason for exclusion. Any disagreement between the review authors were resolved through discussion until a consensus was reached between the reviewers.

Table 1. Inclusion criteria for systematic search

Population	ARDS in patients diagnosed with COVID-19 or due to other etiologies, all age groups
Intervention / Exposure	Extracorporeal Membrane Oxygenation (ECMO), either VA or VV, alone or as an adjunct to mechanical ventilation
Comparator	Mechanical ventilation alone
Outcomes	Survival Hospitalization days Resolution of symptoms Incidence of adverse events
Study Designs	Systematic reviews (SRs), with or without meta-analysis; Rapid reviews (RR)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, no abstract or full text available, or were not the most recent systematic review available which is defined as the systematic review with the latest last search date. Studies which evaluated the effectiveness of ECMO on ARDS secondary to cardiogenic shock alone were also excluded.

4.3. Data extraction and Management

The following information were extracted from the included studies/guidelines/references:

Table 2. Data extracted from the included treatment guidelines, reviews, and studies

Local and International Guidelines	◦ Country of Origin ◦ Section of the guideline where ECMO was mentioned, including indications if available
Reviews from HTA agencies	◦ Country of Origin ◦ Originating agency of the reports/ recommendations/ positions ◦ Conclusion/ Recommendation
Clinical Efficacy or Effectiveness Studies	◦ Author, Year ◦ Period of systematic search ◦ Electronic databases used ◦ Conflict of interest ◦ Funding ◦ Population (with COVID-19 or without COVID-19) ◦ Intervention ◦ Comparator ◦ Outcomes o survival o mortality o hospitalization o time to decannulation o adverse events

	◦ Study design of included studies, number of studies included per study design, risk of bias tool used per study design ◦ results of risk of bias assessment of included studies, total number of subjects included, treatment effect measure reported, GRADE assessment result, critical appraisal result ◦ Meta-analysis results and the study design of the pooled studies, number of studies included per pooling, total number of subjects included per pooling, measures of heterogeneity, assessment results of publication bias. For ongoing or future trials: • Study ID & Title (Author, Year) • Status • Expected Study Completion Date • Study Design • Population (Location) • Intervention • Comparator • Outcomes measure

4.4. Critical Appraisal

The included systematic reviews were appraised independently by two review authors using "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR 2). Further, critical appraisal of an included primary study was done using "The Evaluation of Articles on Therapy" (Dans, A., Dans L., Silvestre, 2017) tool which covers appraisal of articles' validity, results, and acceptability. Any disagreement between the review authors were resolved with a third reviewer as an arbiter.

4.5. Data Synthesis

As this is a rapid review of reviews, qualitative synthesis and quantitative synthesis were intended to be performed as appropriate. DerSimonian and Laird random effects models to conduct the meta-analyses was intended to be used if the characteristics of included studies were deemed appropriate for pooling. All analyses were intended to be performed in RevMan 5.3. Study weights were intended to be generated using the inverse variance method. Risk ratios were intended to be used for dichotomous outcomes, while mean differences or standardized mean differences were intended to be used for continuous outcomes. In all pooled effects, 95% confidence intervals (CIs) were intended to be used.

The I2 statistic was intended to be used to measure heterogeneity between studies. An I2 value of 0-30%, 31-50%, 51-75%, and 76-100% indicate insignificant heterogeneity, moderate heterogeneity, substantial heterogeneity, and considerable heterogeneity, respectively. These ranges and interpretations were adapted from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Sources of heterogeneity were intended to be explored by doing various subgroup analysis based on the pre-identified variables when sufficient data were available. This included special populations (i.e., patients with pre-existing conditions).

5. SUMMARY OF EVIDENCE

5.1. Review of Guidelines and synthesized evidence from HTA agencies

5.1.1 Review of Guidelines

Of the 15 COVID-19 treatment guidelines reviewed, nine guidelines (WHO, Philippines, Australia, Canada, China, Indonesia, Japan, United Kingdom- National Health Service, and United Stated -National Institutes of Health) cited the use of ECMO. On the other hand, we found one guideline (Japan) with explicit statement on contraindication for ECMO use among COVID-19 patients. Meanwhile, the national treatment guidelines of Malaysia and Singapore did not mention the use of ECMO in COVID-19 patients with ARDS. COVID-19 treatment guidelines from the European Union, South Korea, Thailand, and Vietnam were not found. Details on the available treatment guidelines reviewed are in Appendix B.

Among the nine guidelines which included ECMO, the WHO, Australia, Canada, and the US-NIH only issued a moderate or conditional recommendation for the use of ECMO in patients with COVID-19 in ARDS. This is due to the lack of high-quality studies supporting the use of ECMO. On the other hand, the remaining five countries (Philippines, China, Indonesia, Japan and the United Kingdom) did not specify the strength of their recommendation. None of the reviewed countries explicitly stated a strong recommendation for or against the use of ECMO in COVID-19 patients with ARDS.

In general, all the nine identified COVID-19 guidelines recommending ECMO specified reserving the use of the machine once the lung protective ventilation strategy via mechanical ventilation has failed to achieve adequate oxygenation and ventilation. The guidelines from the Philippines, Australia, Canada, Indonesia, and the US-NIH did not detail eligibility criteria for COVID-19 patients with ARDS for whom ECMO is indicated for. Meanwhile, the guidelines from the WHO, China, Japan, and the UK-NHS mentioned specific clinical indicator cut-offs to trigger the use of ECMO which were described in Table 3. Of the four guidelines, the UK-NHS provided the latest and most detailed inclusion and exclusion criteria. These guidelines also noted that prone positioning and optimal lung protective interventions should have been attempted first.

The WHO, Japan, and China all used the ratio of partial pressure of arterial oxygen to the inspired oxygen [PaO2:FiO2 ratio] as a measure of threshold to trigger the use of ECMO. However, the cut-off values for PaO2:FiO2 ratio set by the WHO, Japan, and China are different (i.e., a PaO2:FiO2 of < 50 mmHg for 3 hours, or a < 80 mmHg for > 6 hours by the WHO <100 mmHg for Japan, < 80 mmHg for more than 3-4 hours by China). Meanwhile, the UK-NHS specified the use of multiple scoring systems (i.e. Lung injury score, Clinical Frailty Scale, Respiratory ECMO Survival Prediction [RESP] score) to determine eligibility for the use of ECMO in COVID-19 patients with severe ARDS. The decision of UK-NHS was based on the UK Intensive Care National Audit and Research Center (ICNARC) report that the most unwell COVID-19 patients were not appropriate candidates for ECMO because of their existing comorbidities.

Additionally, Japan explicitly indicated that ECMO is contraindicated for patients aged 65 to 70 or older.

Table 3. Inclusion and exclusion criteria for ECMO eligibility

Country/ Organization	UK- NHS (updated June 2020)	WHO (updated May 2020)	Japan (updated June 16, 2020)	China (updated Mar 2020)
Inclusion Criteria	Potentially reversible severe respiratory failure Lung Injury Score ≥3 or uncompensated hypercapnia with a pH 7.20 or less Failed trial of ventilation in prone positioning ≥ 6 hrs (unless contraindicated) Failed optimal respiratory management / lung protective ventilation Clinical Frailty Scale category ≤ 3 *If RESP Score ≤ 3 ECMO should be considered only after agreement across at least two centers*	In settings with access to expertise in ECMO, consider referral of patients who have refractory hypoxemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO2] to the fraction of inspired oxygen [FiO2] of < 50 mmHg for 3 hours, a PaO2:FiO2 of < 80 mmHg for > 6 hours) despite lung protective ventilation.	ECMO should be considered if there is a progressive deterioration of oxygenation with a PEEP of 10 cmH2O and P/F < 100. Japan ECMOnet for COVID-19 stated in the basic considerations for ECMO management that the prognosis is extremely poor if ECMO is introduced after a long period (more than 7 days) of mechanical ventilation at a high pressure. The prognosis for a patient whose condition is complicated with chronic heart failure, chronic respiratory failure, or other types of chronic organ failure during treatment is worse. Since patients aged from 65 to 70 or more have a poor prognosis, they are generally excluded from ECMO indication in the aforementioned basic notes.	If the outcome of prone position ventilation is poor, ECMO should be considered as soon as possible. Indications include: 1. When Fi02＞90%, the oxygenation index is less than 80 mmHg for more than 3-4 hours; 2. For patients with only respiratory failure when the airway platform pressure ≥ 35cmH2O, VV-ECMO mode is preferred; if circulatory support is needed, VA-ECMO mode should be used. When underlying diseases are under control and the cardiopulmonary function shows signs of recovery, withdrawal of ECMO can be tried.

5.1.2 HTA Agency Findings

Of the 11 HTA agencies reviewed, UK-NICE is the only HTA agency which has a published report on ECMO. The report was a rapid guideline specifically for adult COVID-19 patients needing critical care.

The rapid guideline was created to answer the basic technical and logistical concerns of healthcare professionals and hospital administrators in taking care of a critically ill COVID-19 patient. The guideline includes details on the admission to hospital/ critical care, clinical decision making, and critical care referral algorithm. From their assessment, ECMO can be used to manage severe acute respiratory failure as advised by intensive care clinicians when conventional intensive management has failed. No economic evaluation was performed in the creation of this rapid guideline. Details on the review of UK-NICE can be found on Appendix C.

5.2. Clinical efficacy/ effectiveness and safety of ECMO

5.2.1 Quantity of included studies

Figure 1 summarizes the flow of the systematic search conducted. PubMed search provided a total of 1,368 records while the search for ongoing or future trials or studies in clinicaltrials.gov yielded 13 records, with a total of 1381 records identified. After removing the duplicates, 1,380 remained which were screened against the eligibility criteria using their titles and abstracts. After which, 44 reviews and primary studies were identified for full text screening. The most recent SRs (with or without meta-analysis) for COVID-19 and non-COVID-19 populations were included; hence, the inclusion of two SRs (Haiduc et al., 2020; Aretha et al., 2019) in this review. Technically, the SR on ECMO among COVID-19 patients with ARDS did not meet the eligibility criteria as it did not specify the comparators in the study but was opted to be included in this rapid review as it is the only SR on ECMO among COVID-19 patients with ARDS, to date. In addition, a published primary study on COVID-19 patients with ARDS (Mustafa et al., 2020), which was not covered by the most recent SR on ECMO among COVID-19 population with ARDS, was also included. As it is a case series, it also did not meet the eligibility criteria due to lack of a comparator but was similarly considered in this review for the same reason that there are few ECMO studies specific on COVID-19 patients. Eight on going or future studies or trials were also included in the review. As such, a total of 11 studies were included (3 completed studies composed of 2 reviews and 1 case series; and 8 ongoing or future trials/studies).

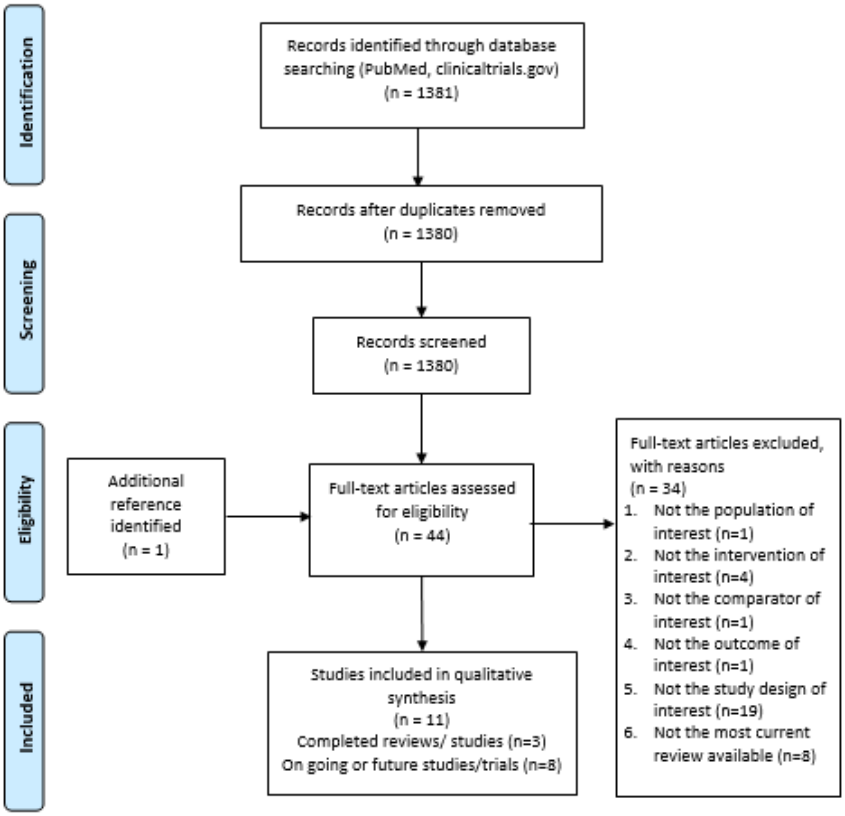

Figure 1. Study (PRISMA) flow diagram of systematic search for synthesized evidence of ECMO

5.2.2 Characteristics of studies and trials

5.2.2.1. Completed studies

Of the three completed studies in this rapid review, two studies were systematic reviews. One involved COVID-19 patients with ARDS (Haiduc et. al., 2020) and the other, non-COVID-19 patient with ARDS with unspecified etiology (Aretha et. al., 2019). Other characteristics of patients enrolled in the studies included in these systematic reviews such as race, age and sex were also not reported. The remaining study was a case series on the use of ECMO in 40 COVID-19 patients with ARDS with mean age of 48.4 years. Among these 40 patients, 30 are males and 10 are females. The patients are predominantly African American (40%), followed by Hispanic (35%) and Caucasians (20%) (Mustafa et al., 2020). As expected, there is more evidence in the use of ECMO among non-COVID-19 patients with ARDS.

In terms of the intervention implemented in the studies, all three studies focused on assessing VV or VA ECMO with Aretha et al. also including $ECCO_2R$ as an intervention. As for the comparator, only Aretha et al. specified the comparators used in the included studies which are no comparator, no ECMO, or mechanical ventilation alone.

All three studies measured mortality as its outcome. In addition to this, Mustafa et al. also measured the length of hospital stay and time from ECMO initiation to ECMO decannulation, while Aretha et al. also measured the risk of bleeding and barotrauma/

pneumothorax as adverse events. None of the studies reported the time to resolution of symptoms and their length of follow-up time or duration.

Both SRs included all types of study designs (i.e., RCT and observational studies). Aretha et al. included seven RCTs, two quasi-RCTs, and eight cohort studies (six of which had unmatched cohorts while the remaining two had matched cohorts). Haiduc et al. included a total of 25 studies consisting of thirteen case studies, seven retrospective cohort studies, one observational cohort study, three cross sectional studies, and one letter to the editor. Overall, the evidence on the efficacy or effectiveness of ECMO on COVID-19 patients were mostly observational studies. Meanwhile, there is a mix of RCTs and non-randomized studies in the included evidence for the effect of ECMO on ARDS in non-COVID-19 patients.

Table 4 elaborates the characteristic of included completed studies.

Table 4. Characteristics of included completed studies

Author, Year	Period of syste-matic search/ duration of study*	COI declar ed? (Y/N)	Databases searched	Population	Intervention	Comparator	Outcome	Study designs included/ Study design*	Correspondi ng number of included studies per study design
Haiduc, 2020	No infor-mation	N	Global Health EMBASE Medline Cochrane databases	COVID-19 patients with ARDS	VV-ECMO/VA-ECMO	not specified	mortality	Retrospective cohort	7
								Cohort studies (observational)	1
								Cross sectional	3
								Case series	6
								Case control	1
								Case report	6
								Letter to the editor	1
Mustafa, 2020*	March 17 to July 17, 2020	Y	N/A	COVID-19 patients with severe respiratory failure supported by ECMO	VV-ECMO	None	mortality, hospital stay, time to decan-nulation	Case series	1
Aretha, 2019	Septemb er 2018-May 2019	Y	PubMed Web of Science Cochrane library EMBASE	Patients with acute hypoxemic respiratory failure/ARD S/ severe ARDS, etiology unspecified	ECLS ($ECCO_2R$ or VV-ECMO/ VA-ECMO with or without intermittent mandatory ventilation)	No comparator/ no ECMO/ IMV alone	Hospital mortality/ ICU mortality/ 6-month mortality, adverse events	RCT	7
								Quasi-RCT	2
								Matched cohort study	2
								Unmatched cohort study	6

Note: VV-ECMO: Veno-venous Extracorporeal Membrane Oxygenation; VA-ECMO: Veno-arterial Extracorporeal Membrane Oxygenation; ECCO2R: Extracorporeal Carbon Dioxide Removal; IMV: Invasive Mechanical Ventilation N/A- not applicable, NR- not reported
For all three studies, no data available for the mean follow up time.

5.2.2.2. On-going and future studies

The database of clinicaltrials.gov was also accessed to searched for ongoing clinical trials. The search revealed that as of August 20, 2020 there are currently eight clinical trials related to the research question. Of the eight detected on-going and future trials on the use of ECMO for COVID-19 patients with ARDS, one (NCT04341285) is not yet recruiting, six (NCT04405973, NCT04397588, NCT04446286, NCT04366921, NCT04383678, NCT04340414) are currently recruiting, and one (NCT04343404) has been recently completed. The target study completion dates of the trials range from August 18, 2020 to April 2021. The completed study (NCT04343404) did not report their outcomes and a manuscript was not available. From the eight, seven are observational studies and one (NCT04341285) was a randomized controlled clinical trial which compares early versus late use of ECMO in COVID-19 patients with severe ARDS. The seven observational studies did not have a comparator stated in their registered protocol. The most common primary outcome measure was mortality rate. A detailed table of the characteristics of future and ongoing trials are included in the Appendix D.

5.2.3. Findings of the included studies in this review

5.2.3.1. Reported risk of bias of the included studies in the systematic reviews

The two systematic reviews included utilized different instruments to assess the risk of bias of their included studies.

Haiduc et al., the SR on COVID-19 patients with ARDS mentioned using the NIH quality assessment tool for all its included studies. Upon our review of the tool, we noted that there were no NIH assessment tools for case reports and a letter to the editor which are study designs/ publication document types included in this SR. Furthermore, the SR did not report the results of the risk of bias assessment and the overall quality of evidence of each of the studies included. Consequently, the impact of the risk of bias assessment of the studies on the result of the systematic review was also not discussed in their manuscript.

Aretha et al., the SR on non-COVID-19 patients with ARDS, used the Cochrane collaboration Risk of Bias (RoB) instrument in the assessment. The authors did not report the RoB rating per domain and only the overall RoB rating of the included primary studies were reported. The six included RCTs and two included quasi- RCTs were deemed to have low risk of bias. The same instrument was also used for the assessment of eight included observational studies which were deemed to have a high risk of bias.

Overall, the primary included studies on the SR among COVID-19 patients were of unknown RoB rating, while the RoB of the primary studies included in the SR among non-COVID-19 patients were highly varied. The included clinical trials, either randomized or non-randomized were rated as low risk of bias, while included observational studies were of high risk of bias (n=8) as rated by the authors of the SR which might be due to the unsuitable risk of bias tool applied. However, the low risk of bias rating for the studies classified as non-randomized clinical trials (quasi- RCTs) were deemed questionable. First, non-randomized clinical trials generally have a high risk of selection bias. Moreover, upon review of these studies, it was found out that they are observational studies which also have an innate high risk of bias.

Table 5 presents the reported ROB assessment of the 2 SR. Note that the RoB ratings shown are based on the ratings by the Haiduc et al. and Aretha et al. No explanation was provided as to how the review authors arrived at such ratings as detailed results of their risk of bias assessments were not reported or discussed.

Table 5. Reported risk of bias assessment of the systematic review

Author of the Systematic Review (Year)	Study designs included	Corresponding number of included studies per study design	Tool used for assessing RoB per study design	Author of the included study (Year)	Overall RoB Rating
Haiduc (2020)	Retrospective cohort	8	NIH Quality assessment tool	Barrasa, 2020	NR
				Chen, 2020	NR
				Loforte, 2020	NR
				Marullo, 2020	NR
				Ruan, 2020	NR
				Wu, 2020	NR
				Yang, 2020	NR
				Zhou, 2020	NR
	Cross sectional	3	NIH Quality assessment tool	Guan, 2020	NR
				Huang, 2020	NR
				Jacobs, 2020	NR
	Case series	6	NIH Quality assessment tool	Li, 2020	NR
				Shen, 2020	NR
				Sultan, 2020	NR
				Wang, 2020	NR
				Zangrillo, 2020	NR
				Zeng, 2020	NR
	Case control	1	NIH Quality assessment tool	Tang, 2020	NR
	Case report	6	Not applicable	Bemtgen, 2020	NR
				Firstenberg, 2020	NR
				Hartman, 2020	NR
				Nakamura, 2020	NR
				Taniguchi, 2020	NR
				Zhan, 2020	NR
	Letter to the editor	1	Not applicable	Takeda, 2020	NR
Aretha (2019)	RCT	6	Cochrane Collaboration risk-of-bias instrument	Zapol, 1979	Low
				Morris, 1994	Low
				Peek, 2011	Low
				Bein, 2015	Low
				Combes, 2019	Low

				REST trial (on going)	N/A
	Quasi-RCT	2		Noah, 2011	Low
				Pham, 2013	Low
	Matched cohort	2		Kanji, 2016	High
				Tsai, 2015	High
	Unmatched cohort	6		Lewandowski, 1997	High
				Mols, 2000	High
				Beiderlinden,2006	High
				Davies, 2009	High
				Roch, 2010	High
				Patroniti, 2011	High

Note: NR: not reported, RCT: Randomized Controlled Trial; RoB: Risk of Bias

5.2.3.2. Quantitative results of the included studies

We did not perform quantitative synthesis primarily due to the differences in the population (COVID-19 patients: Mustafa et al., 2020; Haiduc et al., 2020 versus non-COVID-19 patients: Aretha et al., 2020), comparator (No comparator: Haiduc et al., 2020; Mustafa et al., 2020 versus No ECMO/IMV alone: Aretha et al., 2020), and study designs. Studies which had similar populations (Haiduc et al 2020; Mustafa et al 2020) were also not pooled due to unspecified patient characteristics and intervention (i.e. no specified eligibility criteria or severity of ARDS in patients enrolled, no specified timing of ECMO initiation).

As such, we noted below the evidence for clinical efficacy / effectiveness and safety of ECMO based on the reported findings in the studies:

- **Survival**

  Among COVID-19 patients with ARDS, the reported mortality of patients who used ECMO was 19.83% (95/479), as reported by the SR of Haiduc et al., combining the results of 25 observational studies (n=3428). This was computed using the following formula: combined ECMO-associated deaths from all studies divided by the total number of patients who required ECMO from all studies. The mortality rate among patients who did not receive ECMO was not reported, thus the risk ratio with the confidence intervals cannot be calculated. Meanwhile, the case series by Mustafa et al. among COVID-19 patients who received ECMO observed a relatively lower overall mortality rate of 15% (6/40). As these findings only report the outcomes among ECMO users, the current evidence cannot demonstrate whether the use of ECMO is better than mechanical ventilation among COVID-19 patients with ARDS.

  For the non-COVID specific evidence (i.e., any ARDS patients who are non-COVID-19 infected), the use of ECMO resulted in non-significant increase in mortality rate in patients with ARDS reported by Aretha et al. [OR: 2.23, 95%CI (0.18, 28.07)] from two RCTs. The I^2 was 92.74% (p-value <0.001) which indicates considerable heterogeneity between the two studies.

  When the findings of the two quasi-RCTs together with the two RCTs were pooled together, the use of ECMO appears to have a significant effect on reducing the

odds of mortality in patients with ARDS [OR: 0.51, 95%CI (0.38, 0.59)]. The I^2 was at 12.22% (p-value = 0.33) which suggests that the pooled studies have insignificant heterogeneity. However, note that upon our review of these reported quasi-RCTs, it was found out that they are observational studies. Hence, caution should be observed in interpreting this pooled estimate.

The authors also performed a meta-analysis on mixed study designs (two RCTs, two quasi-RCTs and four prospective observational trials) which showed a pooled treatment effect of OR: 0.96, 95%CI (0.52, 1.77), which suggests marginal overall mortality benefit in using ECMO compared to conventional mechanical ventilation (Aretha et al, 2019). The I^2 was 82.95% (p-value <0.001) which indicates considerable heterogeneity from the two studies. The high heterogeneity may be due to the different study designs, populations, and other interventions that are adjunct to the treatment of severe ARDS.

We also note that the source of heterogeneity was not investigated by the authors of this review.

- **Hospitalization days**
  Only Mustafa et al. reported the mean duration of hospitalization which was observed to be 44.5 days (n=29). We noted that this result was not based on the outcomes of all patients included in the study as these were taken from 29 patients only.

- **Duration of ECMO treatment**

  Only Mustafa et al. reported the mean duration of ECMO treatment (i.e., the time it takes from initiation of ECMO to ECMO decannulation), which was 29.9 days (95% CI: 24.4-35.9 days). Similar to the previous outcome reported by this study, it should be noted that the mean hospitalization and mean duration of ECMO were not based on the outcomes of all patients included in the study as these were taken from 29 patients only. The characteristics and clinical outcomes of each patient were not individually identified which suggests reporting bias.

- **Resolution of symptoms**
  None of the included studies in this review evaluated the effect of ECMO on resolving symptoms.

- **Incidence of adverse events**
  This review did not find safety evidence of ECMO involving COVID-19 patients as only Aretha et al., the SR among non-COVID19 ARDS patients, reported the incidence of adverse events.

  Its findings were based, however, on a meta-analysis of studies with different study designs (two RCTs, two quasi-RCT, two observational studies) which evaluated the adverse events in patients which received ECMO versus mechanical ventilation which were moderately heterogenous (I^2 = 37.06%; p-value = 0.16). The pooled treatment effect suggests that ECMO significantly increases the odds of patients having bleeding episodes compared to conventional mechanical ventilation by almost three times more [OR: 2.93, 95% CI (1.84, 4.68)]. Additionally, it was estimated that ECMO may result in a non-statistically significant increase

in the odds of barotrauma and/or pneumothorax. [OR: 2.38, 95% CI (0.84, 6.75)]. The treatment effect estimates were pooled from different study designs that may have contributed to the considerable heterogeneity (I^2=68.2%, p-value = 0.04). In addition to this, it should also be noted that one of the studies included in the pooling used extracorporeal carbon dioxide removal ($ECCO_2R$) which is a variation of the ECMO intervention (Morris, 1994).

The results of the three studies are outlined in Table 5.

Table 6. Reported quantitative results of included systematic reviews and primary study

Author of the SR (Year)	Population	Intervention	Compa-rator	Outcome	Study design	Num. of studies included (N)	Statistical model (fixed/ random effect)	Hetero-geneity (I2 %, p-value, S/NS)	Reported treatment effect) (RR/ OR/ % with 95% CI)	Publication bias (method)
Haiduc (2020)	COVID-19 patients with ARDS	VV-ECMO, VA-ECMO	NR	overall mortality (% mortality= number of ECMO associated deaths from all studies /total number of patients that required ECMO from all studies)	SR which included observational studies (Retrospective cohort, case control studies, cross sectional studies, case series, case reports, letter to the editor)	25 (3428)	N/A	N/A	19.83% among ECMO users only (no CI reported); % mortality among non-ECMO users was not reported	N/A
Mustafa (2020)	COVID-19 patients with severe respiratory failure supported by ECMO	VV-ECMO	NR	Mortality (% mortality = number of deaths/ total population followed) x100)	case series	1 (40)	N/A	N/A	15 % among ECMO users only (no CI reported)	N/A
				mean hospital stay (days)		1 (29)			44.5 (40.37, 48.63)	
				Mean ECMO duration (days)		1 (32)			29.9 (24.4, 35.9)	
Aretha (2019)	Patients with acute hypoxemic respiratory failure/ARDS/ severe ARDS	ECLS (ECCO2R or VV-ECMO/ VA-ECMO with or without intermittent mandatory ventilation)	NR	In-hospital Mortality (OR)	SR which included mixed study designs (2 RCT, 2 Quasi RCT, 4 Observational studies)	8 (1497)	random effects model	82.95% (<0.001), S	OR 0.96 (0.52, 1.77), NS	Funnel Plot, symmetrical (not presented); Egger's test = 0.33)
				In hospital Mortality (OR)	Mixed (2 RCT, 2 Quasi-RCTs)	4 (839)	fixed effect model	12.22% (0.33), NS	OR 0. 51 (0.28, 0.69), S	
				In hospital Mortality (OR)	RCTs	2 (429)	random effects model	92.74% (<0.001), S	OR 2.23 (0.18, 28.07), NS	
				Adverse events (Bleeding) (OR)	Mixed (2 RCT, 2 Quasi RCT, 2 Observational studies)	6 (839)	fixed effect model	37.06% (0.16), NS	OR 2.93 (1.84, 4.68) S	
				Adverse events (Pneumothorax/Barotrauma) (OR)	Mixed (2 RCTs, 1 Observational Study)	3 (411)	Random effect model	68.20% (0.04) S	OR 2.38 (0.84, 6.75) NS	

Note: VV-ECMO: Veno-venous Extracorporeal Membrane Oxygenation; VA-ECMO: Veno-arterial Extracorporeal Membrane Oxygenation; ECCO2R: Extracorporeal Carbon Dioxide Removal; N/A- not applicable, NR- not reported
Mean follow up period and GRADE assessment were not reported by all three studies.

5.2.4. Critical Appraisal of the included studies

Of the three studies that were critically appraised, the studies of Haiduc et al. and Aretha et al. were appraised using the AMSTAR2 tool while the study of Mustafa et al. was appraised using the Evaluation on Articles of Therapy by Dans et al. (2017).

The two systematic reviews both had an overall rating of critically low. Both reviews failed to satisfy the critical domains for protocol registration, adequacy of literature search and justifying exclusion of studies. Haiduc et al. also failed to establish the effect of the risk of bias on the results of the study and did not specify the comparator for its review. Aretha et al., on the other hand, failed to establish the effect of the risk of bias for the non-randomized studies only. Moreover, we noted several pooled estimates from different study designs without any justification and discussion on its impact on the interpretation of their observed treatment effect.

Mustafa et al. was rated with low internal validity owing to the inherent limitation of the study design which does not have a comparator arm, randomization, nor blinding. Further, the applicability of the results of the study may be limited due to the study population not having similar baseline characteristics (i.e. predominantly African Americans, predominantly male). Results of the critical appraisal of the included studies are detailed in Appendix E.

5.3. Resource requirements

The WHO, Australia, Canada and US-NIH recognized that the implementation and use of ECMO is resource-intensive and needs highly specialized equipment, infrastructure, and personnel. The authors were also able to inquire from a specialist in one of the national specialty centers about resource requirements in detail.

According to responses to an inquiry from the National Kidney Transplant Institute, as of August 24, 2020, there are eight hospitals with functional ECMO machines. It was not specified whether they have assigned machines specific for the use of COVID-19 patients. It should be noted that only one out of all the available ECMO machines is available outside the National Capital Region (NCR), which is in Region XI in Davao City.

Table 7. List of hospitals with ECMO machines

Hospital	Hospital type	Number of ECMO machines	Location
1. National Kidney and Transplant Institute (NKTI)	Public	3	Metro Manila
2. Lung Center of the Philippines (LCP)	Public	3	
3. Philippine Heart Center (PHC)	Public	2	
4. St. Luke's Medical Center (SLMC)	Private	1	
5. Asian Hospital	Private	1	
6. Makati Medical Center (MMC)	Private	1	
7. The Medical City (TMC)	Private	1	

8. Southern Philippines Medical Center (SPMC)	Public	1	Davao
Total nationwide		13	NCR: 12 Region XI: 1

Infrastructure and Equipment
The insertion of VV-ECMO can be performed inside the intensive care unit (ICU). The room must have sufficient room for at least four people at any one time, and the following equipment: ECMO machine, mechanical ventilator, hemodialysis machine, telemetry and EEG machine. Additionally, the following equipment may be placed as needed: endoscopy unit, echo/ ultrasound/ x-ray machine, intra-aortic balloon pump machine.

Human Resource
Optimal use of ECMO also requires attention and expertise of different hospital personnel. Table 8 lists the required personnel in using ECMO and their specific roles in the treatment regimen.

Table 8. Manpower requirement in using ECMO

	Personnel	Details
3	Pulmonologist/ intensivists	For management of oxygenation and ventilation
3	Thoracic and cardiovascular surgeon	For cannulation and decannulation
3	Anesthesiologist	During cannulation and throughout ECMO period to maintain sedation
3	Cardiologist	For heart assessment and monitoring
6	ICU nurses (2 nurses per shift)	For monitoring and daily care
3	Respiratory therapist	For administration of respiratory interventions
3	Perfusionist (1 perfusionist per shift)	For adjusting ECMO settings based on patient's heart and lung support needs

Blood, blood products, and other fluids
The use of ECMO machines also requires multiple units of blood products per day. This need would be challenging to satisfy because most of the blood donation activities during the quarantine were cancelled or limited. Additionally, there would be increased costs in screening probable donors for COVID-19 infection.

Table 9. Fluids requirement in ECMO use

Fluids	Daily needs
Intravenous Fluids	2-3 liters
Packed Red Blood Cell	1-2 units
Fresh Frozen Plasma	2-3 units
Platelet Concentrate	3-5 units

The availability of all blood products must always be ensured once ECMO has been initiated.

COVID-19 specific arrangements
Aside from the resource requirements stated above, the use of ECMO machines involves additional adjustments for COVID-19 patients. These include the assignment of COVID-19 and non-COVID-19 ECMO patients in different wards, the use of level 4 personal

protective equipment (PPE) for all personnel, quarantine of the staff every 7 days, daily room disinfection, installation of high efficiency particulate air (HEPA) filters and construction of negative pressure rooms. There are at least 3 hospitals in the country which can potentially accommodate COVID-19 patients that would require ECMO: NKTI, LCP, and PGH.

Cost estimates

Table 10 shows the actual hospital costs which are calculated from a sample size of 21 patients admitted from June 2018 to March 2020. All patients were non-COVID-19 patients, with an average age of 33 years old, and are under the service financial classification.

Table 10. Actual hospital cost of using ECMO from the National Kidney Transplant Institute

	Mean	Median	Lower limit	Upper limit
Cost per day (PhP)	371,133.88	302,831.33	146,574.70	1,228,247.07
Length of hospital stay (days)	11	8	1	37
Total hospital charges (PhP)	3,120,642.27	3,147,273.00	1,228,247.07	5,999,845.06

Correlation between different patient factors such as age, number of days in ECMO, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score and, Sequential Organ Failure Assessment (SOFA) score and cost of treatment was determined using costing data from actual hospital bill charges of 20 service patients from NKTI. The patients all have a diagnosis of leptospirosis with severe ARDS. Based on visual inspection of the scatter plot, the data suggests that there is no apparent relationship between aforementioned factors and the cost of treatment (Figure 2).

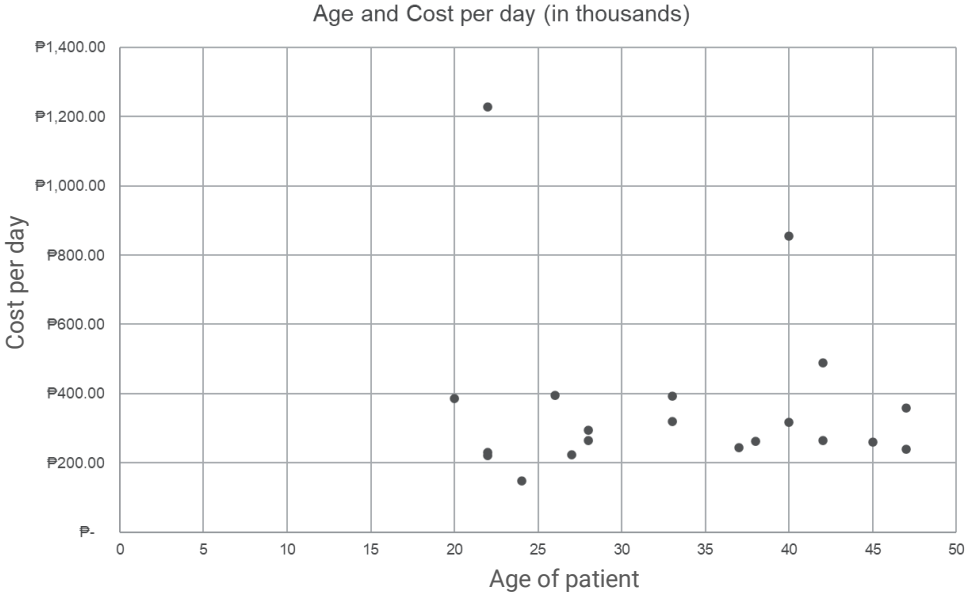

Figure 2. Scatterplot showing relationship between age of patient and cost of ECMO treatment per day

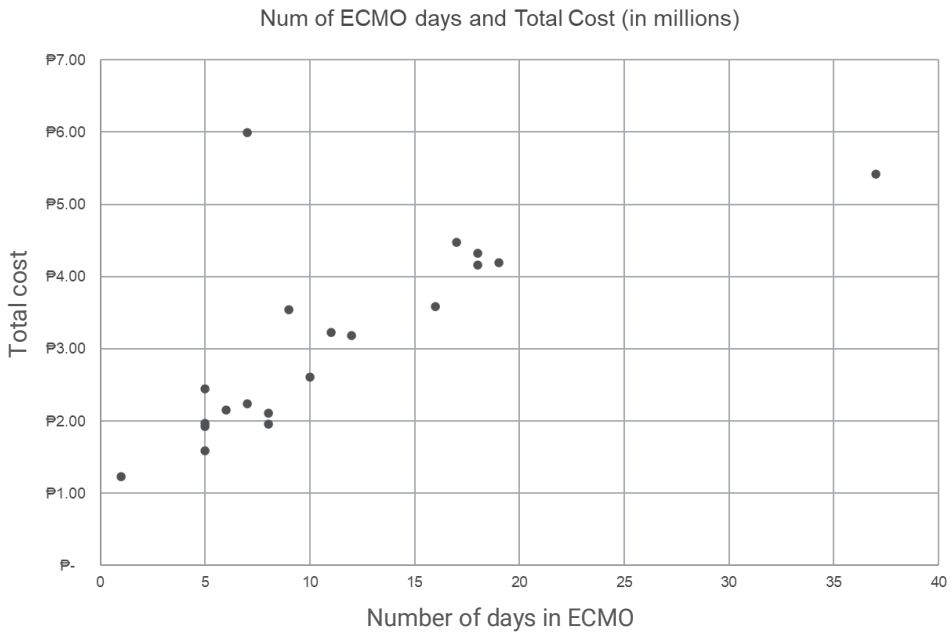

Figure 3. Scatter plot showing relationship between number of days in ECMO and cost of ECMO treatment per day

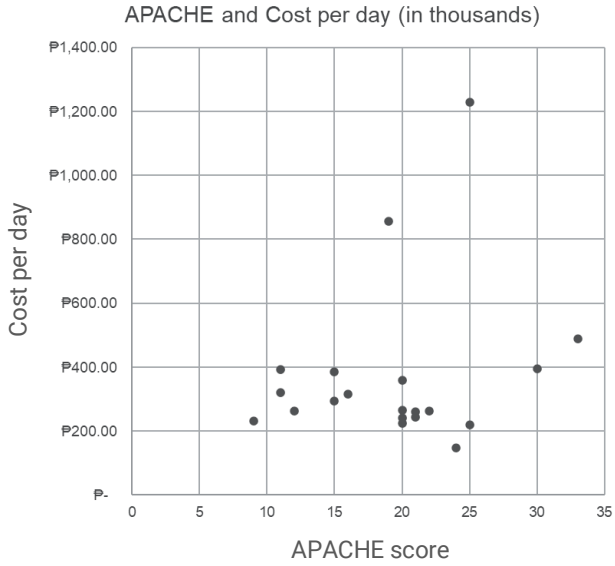

Figure 4. Scatter plot showing relationship between APACHE score of patients and cost of ECMO treatment per day

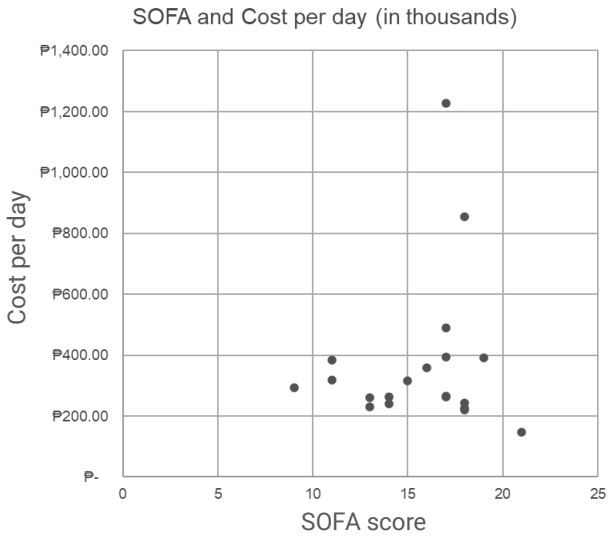

Figure 5.Scatter plot showing relationship between SOFA score of patients and cost of ECMO treatment per day

6. LIMITATIONS

This review recognizes the following limitations: first, as this is a rapid review, certain steps of a systematic review were abbreviated such as searching through other search databases. The study was also limited to the most recent systematic reviews and a relevant case series for COVID-19. Although a more recent primary study was also included, other primary studies which were not covered by the most recent systematic review by Haiduc et. al (2020) were not included in this review due to time constraints.

7. CONCLUSION

GUIDELINE RECOMMENDATION AND EVIDENCE SYNTHESIS FROM HTA AGENCIES

Which countries have implemented ECMO for the management of ARDS secondary to COVID-19 infection?

Of the 15 guidelines reviewed, nine guidelines from the WHO, Australia, Canada, China, Indonesia, Japan, Philippines, US-NIH, and the UK-NHS recommended the use of ECMO in COVID-19 patients. The WHO, Australia, Canada, and the US-NIH issued a moderate to conditional recommendation for severe ARDS in COVID-19. Meanwhile, the Philippines, China, Indonesia, Japan, and the UK-NHS also recommended ECMO after failure of mechanical ventilation, but the countries did not specify the strength of their recommendation. These guidelines generally recommend that ECMO should be reserved once the lung protective ventilation strategy via mechanical ventilation has failed to achieve adequate oxygenation and ventilation.

What is the current position/ recommendation of HTA agencies regarding the use of ECMO for the management of ARDS secondary to COVID-19 infection?

UK-NICE is the only HTA agency which has a published rapid guideline on ECMO which mainly specified treatment for adult COVID-19 patients needing critical care. Based on their assessment, ECMO can be used to manage severe acute respiratory failure as advised by

intensive care clinicians when conventional intensive management failed. No economic evaluation was performed in the creation of this rapid guideline.

CLINICAL EFFICACY / EFFECTIVENESS AND SAFETY

Among critically ill COVID-19 patients with acute respiratory distress syndrome, is ECMO alone or combined with mechanical ventilation compared to mechanical ventilation alone effective and safe in improving the survival rate, decreasing the hospitalization days, resolving the symptoms and decreasing the incidence of adverse events?

Currently, there is insufficient evidence to support the use of ECMO in improving survival rate and decreasing hospitalization days among critically ill COVID-19 patients with acute respiratory distress syndrome given the current limited number of evidence and the absence of control groups in the current studies which cannot demonstrate relative treatment effect. There was no evidence found on the effect of ECMO in resolving symptoms of ARDS. There were also no outcomes reported in terms of risks for adverse events from existing evidence on its use for COVID-19 patients.; hence, we cannot establish the safety of ECMO among COVID-19 patients.

Looking at existing evidence on the use of ECMO among non-COVID-19 patients with severe ARDS, the latest relevant systematic review revealed that ECMO did not result in significant improvement in the survival rate of patients with ARDS. No evidence was found in terms of decreasing hospitalization days and resolution of symptoms for the non-COVID-19 population. Additionally, there was a significantly increased risk for bleeding associated with the use of ECMO in patients with severe ARDS while there was no significant increased risk for barotrauma or pneumothorax was associated with ECMO use. However, it should be noted that findings for adverse events were based on estimates from pooling studies of different study designs without justification of pooling from the reviewers, and with considerable heterogeneity. Hence, caution must be observed in interpreting such pooled estimate. Also note that the pooled treatment effect for adverse events included a study which also evaluated extracorporeal carbon dioxide removal ($ECCO_2R$) which is a variation of the ECMO intervention (Morris, 1994).

Critical appraisal of these three studies revealed a critically low rating (using AMSTAR 2) for the two systematic reviews by Haiduc et al. (2020) and Aretha et al. (2020), and low internal validity and applicability (using the appraisal tool by Dans et al., 2017) for the included case series by Mustafa et al. (2020).

On-going and future trials are anticipated to provide stronger and more conclusive evidence on the relative treatment effect of using ECMO to manage ARDS among COVID-19 patients.

Resource requirements

What are the technical, infrastructure, logistical and organizational needs in implementing ECMO for COVID-19 patients with ARDS?

There are only 13 ECMO machines nationwide, with 12 of them in Metro Manila, and only one located in Davao City. The 13 machines are in eight hospitals (4 public and 4 private). The use of ECMO would need a fully equipped intensive care unit (ICU), with negative pressure ventilation if used for a COVID-19 patient. A patient would need at least five specialist doctors and four allied health staff per shift (three shifts per day). There is a daily need for multiple units of different blood products.

Based on previous hospitalization data on non-COVID-19 patients from NKTI in June 2018 to March 2020 (n=21), the use of ECMO would need an average of Php 4,082,472.68 for an average

11-day ECMO use per patient in the service classification, based on the submitted information from NKTI. Additionally, the acquisition cost of each ECMO machine is around 8 to 10 million based on DOH-HFDB data.

Overall, there is insufficient evidence to conclude that the use of ECMO will confer benefits in neither COVID-19 nor non-COVID-19 patients with severe acute respiratory syndrome in terms of improving mortality rate, length of hospital stay and resolution of symptoms. Additionally, using this health technology for COVID-19 patients with severe ARDS might potentially place additional strain on current healthcare resources.

8. DECLARATION OF CONFLICT OF INTERESTS

The reviewers declare that they have no competing interests.

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10. APPENDICES

Appendix A. Systematic search terms

	Population	Intervention	Comparator	Outcome
Search terms	COVID-19, severe acute respiratory syndrome coronavirus 2, ards, human	extracorporeal membrane oxygenation, extracorporeal membrane oxygenations, oxygenation, extracorporeal membrane, oxygenations, extracorporeal membrane, extracorporeal membrane oxygenation, extracorporeal membrane oxygenations, oxygenation, extracorporeal membrane, oxygenations, extracorporeal membrane	N/A	N/A

Appendix B. Local and International Guidelines

Countries	Findings	Reference
WHO	**[Conditional Recommendation]** **Clinical management of COVID-19: Interim guidance [May 27, 2020]** **Recommendations for adult and pediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation:** • In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO2] to the fraction of inspired oxygen [FiO2] of < 50 mmHg for 3 hours, a PaO2:FiO2 of < 80 mmHg for > 6 hours) despite lung protective ventilation. **Remarks for adults:** An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade). However, ECMO was associated with a reduced risk of the composite outcome that consisted of mortality and crossover to ECMO treatment, and a post-hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study. ECMO is a resource-intensive therapy and should be offered only in expert centers with a sufficient case volume to maintain expertise and staff volume and capacity to apply the IPC measures required. In children, ECMO can also be considered in those with severe ARDS, although high-quality evidence for benefit is lacking.	https://www.who.int/publications/i/item/clinical-management-of-covid-19
Philippines -PSMID	**[Strength of recommendation not stated.]** **Philippine society for microbiology and infectious diseases:** **Interim guidance on the clinical management of adult patients with suspected or confirmed COVID-19 Infection [Version 3.1, as of July 20, 2020]** Extracorporeal life support (ECLS) should be considered when the above measures are unable to provide adequate oxygenation. Consider referral to a center with access to ECLS. (page 25)	https://www.psmid.org/wp-content/uploads/2020/07/Final-PCP-PSMID-PCCP-COVID-19-Guidelines-20July2020b.pdf

Australia	**[Consensus Recommendation]** **National COVID-19 clinical evidence task force** **Australian guidelines for the clinical care of people with COVID-19** **8.9.1 ECMO for adults** In mechanically ventilated adults with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning), consider using veno-venous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO center. (Consensus recommendation) Benefits and harms: Small net benefit, or little difference between alternatives. Certainty of evidence: No studies were identified in COVID-19 patients that compare ECMO to no ECMO. Patients' preference and values: Substantial variability is expected or uncertain. Resources and other considerations: We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centers, healthcare workers, and infrastructure. Feasibility: Due to the resource-intensive nature of ECMO there are likely to be feasibility issues. ECMO is likely to only be feasible in a limited number of centers.	https://app.magicapp.org/#/guideline/L4Q5An/section/no3vwn
Canada	**[Strength of recommendation not stated.]** **Clinical Management of patients with Moderate to Severe COVID-19: Interim Guidance** **Recommendations for adult and pediatric patients with ARDS in whom a lung protective ventilation strategy fails. [As of April 9, 2020]** In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia despite lung protective ventilation. An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade). However, ECMO was associated with a reduced risk of the composite outcome of mortality and crossover to ECMO, and a post hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study. ECMO should ideally be offered in expert centres with a sufficient case volume to maintain expertise and that can apply the IPC measures required for adult	https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html

	and paediatric COVID-19 patients [Consider – the intervention may be beneficial in selected patients (conditional recommendation) or be careful when considering this intervention.]	
China	**[Strength of recommendation not stated.]** **China's National Health Commission** **Novel Coronavirus Treatment Guidelines – 7th Edition:** 3.2.4 Rescue Therapy: Pulmonary re-tensioning is recommended for patients with severe ARDS. With sufficient human resources, prone position ventilation should be performed for more than 12 hours per day. If the outcome of prone position ventilation is poor, extracorporeal membrane oxygenation (ECMO) should be considered as soon as possible. Indications include: 1.) When Fi02＞90%, the oxygenation index is less than 80mmHg for more than 3-4 hours; 2.) For patients with only respiratory failure when the airway platform pressure ≥ 35cmH2O, VV-ECMO mode is preferred; if circulatory support is needed, VA-ECMO mode should be used. When underlying diseases are under control and the cardiopulmonary function shows signs of recovery, withdrawal of ECMO can be tried.	https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf
Japan	**[Strength of recommendation not stated.]** **Clinical Management of patients with COVID-19, Ver. 2.1; June 16, 2020** Japan ECMOnet for COVID-19 stated in the basic considerations for ECMO management that the prognosis is extremely poor if ECMO is introduced after a long period (more than 7 days) of mechanical ventilation at a high pressure. It also stated that a careful and comprehensive decision is required for the indication of ECMO, a large number of personnel and a considerable work load are required when using ECMO treatment for COVID-19, and ECMO should be considered if there is a progressive deterioration of oxygenation with a PEEP of 10 cmH2O and P/F < 100. ECMO must be withdrawn if a high degree of pulmonary fibrosis develops, and informed consent for withdrawal must be provided prior to its introduction. In addition, ECMO is contraindicated or off-label for patients who have irreversible underlying diseases or are in the terminal stage of cancer. The prognosis for a patient whose condition is complicated with chronic heart failure, chronic respiratory failure, or other types of chronic organ failure in the course of treatment is worse. Since patients aged from 65 to 70 or more have a poor prognosis, they are generally excluded from ECMO indication in the aforementioned basic notes.	https://www.mhlw.go.jp/content/000646531.pdf

Indonesia	**[Strength of recommendation not stated.]** **Ministry of Health of Indonesia** **Guidelines for the prevention and control of coronavirus disease (COVID-19) [July 2020]** For health facilities that have expertise in Extracorporeal Life Support (ECLS), can be considered when patients still have refractory hypoxemia even after lung protective ventilation. Currently there are no recommended guidelines use of ECLS in ARDS patients, however there are studies that ECLS is likely to reduce the risk of death. (Translated from Indonesian)	https://covid19.go.id/storage/app/media/Protokol/REV-05_Pedoman_P2_COVID-19_13_Juli_2020.pdf
Malaysia	**Ministry of Health of Malaysia** **Annex 2e: Clinical Management of Confirmed COVID-19 Case in Adult and Pediatric patients [July 6, 2020]** Although the use of supplemental oxygenation and ventilation was briefly mentioned in the guidelines, no specific mention in the use of ECMO for COVID-19 was specified in the document.	http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_2e_Clinical_Mx_of_Confirmed_Case_in_Adult_and_Paediatric_latest_6_July_2020.pdf
Singapore	**National Center for Infectious Diseases- Singapore** **Interim Treatment Guidelines for COVID-19 [Version 3.0, as of July 6, 2020]** Although ECMO use was briefly mentioned in the context of patients eligible for Remdesivir, the guidelines did not specify the indication for the use of ECMO, and the supporting evidence for its use for severe ARDS in COVID-19 patients. Furthermore, the guidelines did not have detailed instructions for supportive therapy in COVID-19, it only focuses on the drugs for COVID-19.	https://www.ncid.sg/Documents/COVID-19%20Therapeutic%20Workgroup%20-%20Interim%20Treatment%20Guidelines%20for%20COVID-19%20v3%20(6%20July%202020)%20-%20FINAL%20(ed).pdf
UK - NHS England	**Clinical guide for extracorporeal membrane oxygenation (ECMO) for respiratory failure in adults during the coronavirus pandemic [Version 2, June 25, 2020]** Respiratory ECMO is indicated for acute severe but potentially reversible respiratory failure. It is therefore expected that the service will experience increased demand in response to patients with COVID-19.	https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0156-Extra-Corporeal-

	The ICNARC report on COVID-19 in critical care suggests that those who have so far become the most unwell as a result of COVID-19 are often not suitable for ECMO due to underlying health problems and comorbidities. However, patients who meet the following clinical criteria may be considered suitable for ECMO support. Inclusion Criteria (updated June 2020) • Potentially reversible severe respiratory failure • Lung Injury Score ≥3 or uncompensated hypercapnia with a pH 7.20 or less • Failed trial of ventilation in prone positioning ≥ 6 hrs (unless contraindicated) • Failed optimal respiratory management / lung protective ventilation • Clinical Frailty Scale category ≤ 3 • If RESP Score ≤ 3 ECMO should be considered only after agreement across at least two centres Exclusion Criteria • Refractory multiorgan failure • Evidence of severe neurological injury So far, there are seven commissioned centers in England are specifically designated to receive patients that are indicated for ECMO.	Membrane-Oxygenation-ECMO-Adult-Speciality-Guide-1.pdf
US - NIH	**[Moderate recommendation for the statement, Expert Opinion]** **COVID-19 Treatment Guidelines- Critical care- Extracorporeal membrane oxygenation [April 21, 2020]** There is insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia. While ECMO may serve as an effective short-term rescue therapy in patients with severe acute respiratory distress syndrome and refractory hypoxemia, there is no conclusive evidence that ECMO is responsible for better clinical outcomes in patients who received ECMO than in patients who did not receive ECMO. ECMO is used by some experts, when available, for patients with refractory hypoxemia despite optimization of ventilation strategies and adjunctive therapies. Ideally, clinicians who are interested in	https://www.covid19treatmentguidelines.nih.gov/critical-care/extracorporeal-membrane-oxygenation/

	using ECMO should either try to enter their patient into clinical trials or clinical registries so that more informative data can be obtained.	

No guidelines found for the following: European Union, South Korea, Thailand, and Vietnam

Appendix C. HTA agencies with reviews on the use of ECMO for COVID-19

Institution	Findings	Reference
UK-NICE	**COVID-19 rapid guideline: critical care in adults [April 29, 2020]** "Extracorporeal Membrane Oxygenation Be aware that respiratory extracorporeal membrane oxygenation (ECMO) services can advise intensive care clinicians on managing severe acute respiratory failure. Be aware that respiratory ECMO services can accept referrals for critically ill patients where: they have potentially reversible severe respiratory failure optimal conventional intensive care management has failed they meet the eligibility criteria for the respiratory ECMO service."	https://www.nice.org.uk/guidance/ng159/chapter/5-Service-organisation
US- AHRQ	Previously submitted for review in 2018 but was not prioritized.	https://effectivehealthcare.ahrq.gov/system/files/docs/topic-brief-extracorporeal-membrane-oxygenation.pdf

No HTA reports found for the following: EUNetHTA, Australia- MSAC, Canada-CADTH, China, Indonesia-InaHTAC, Malaysia- MAHTAS, Singapore- ACE, South Korea- NECA, Thailand- HiTAP

Appendix D. Characteristics of included ongoing or future trials

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
NCT04405973 Clinical Scores for Outcome Prediction in Patients With Severe COVID-19 Pneumonia Requiring ECMO Alexander Supady, 2020 Recruiting August 31, 2020	single-arm retrospective multi-center registry	(Germany) (N=100 participants) All COVID-19-patients treated on an ICU at the participating centers and requiring VV- ECMO support Inclusion Criteria: patient admitted to ICU initiation of vv-ECMO definite SARS-CoV-2-infection Exclusion Criteria: none	vv-ECMO required in severe COVID-19 ARDS	No comparator	Primary Outcome Measures: overall survival [Time Frame: 30 days] Secondary Outcome Measures: 1. duration of ECMO treatment [Time Frame: 30 days] 2. duration of ventilation treatment [Time Frame: 30 days] 3. duration of initiation of ECMO treatment to ICU discharge [Time Frame: 30 days]
NCT04341285 Early Versus Late ECMO Therapy in COVID-19 Induced ARDS (ECMO-VID) (ECMO-VID) Peter Rosenberger, 2020 Not yet recruiting May 1, 2022	Interventional, randomized, parallel assignment trial	(Germany) (N=200 participants) Inclusion Criteria: -COVID-19 positive (+) ARDS as defined according to the Berlin Definition -ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO2/ FiO2) ≤100 -Bilateral opacities consistent with pulmonary edema on frontal chest radiograph -requirement for positive pressure ventilation via an endotracheal tube or non-invasive ventilation -no clinical evidence of left atrial hypertension, or if measured, a Pulmonary Arterial Wedge Pressure (PAOP) less than or equal to 18 mmHg. -≤ 7 days from the initiation of mechanical ventilation at the time of randomization. - Patients must	Active Comparator: Early ECMO Experimental intervention: Insertion of Extracorporeal Membrane Oxygenation (ECMO) within 24 hours of referral to an Intensive Care Unit.	Active Comparator: Late ECMO Insertion of Extracorporeal Membrane Oxygenation (ECMO) as rescue therapy following failure of conventional therapy for ARDS. This conventional therapy will be standardized to reduce bias.	Primary Outcome Measures: 28 day all-cause mortality [Time Frame: 28 Days] Secondary Outcome Measures: -90 day all-cause mortality [Time Frame: 90 days] -Sepsis-related organ failure assessment score at day 1-14, 28 and 90 days [Time Frame: day 1-14, 28 and 90] -duration of mechanical ventilation support [Time Frame: 28 days] -Ventilator Associated Pneumonia [Time Frame: 28 days] -Bleeding complications [Time Frame: 28 days] -Acute Renal Failure [Time Frame: 28 days] -Discharge Location [Time Frame: 90 days]

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
		be enrolled within 96 hours of onset of ARDS. Exclusion Criteria: -COVID-19 negative (-) ARDS -Age less than 18 years -More than 7 days since initiation of mechanical ventilation -more than 96 hours since meeting ARDS criteria -patient, surrogate or physician not committed to full intensive care support. -pregnancy			
NCT04397588 Extracorporeal Membrane Oxygenation (ECMO) and Coronavirus Disease (COVID) 19 (ECMO-SARS) Nicolas Nesseler, André Vincentelli Recruiting October 21, 2020	Observational, prospective cohort	(France) (N=300 participants) Study Population Critically ill COVID-19 patients with ARDS or/and acute refractory heart failure Inclusion Criteria: All COVID-19 patients, adults or children, Tested positive by RT-PCR for SARS-CoV2 (nasopharyngeal swabs, sputum, endotracheal aspiration, bronchoalveolar lavage or stool sample) and / or with a diagnosis made on chest CT findings, Supported by venovenous or venoarterial ECMO Exclusion Criteria: Temporary legally protected Adults over a set period or waiting for protection supervision, guardianship	ECMO	None	Primary Outcome Measures : Hospital mortality [Time Frame: up to 90 days] Secondary Outcome Measures : -Mortality Day 28 [Time Frame: Day 28] -Mortality Day 90 [Time Frame: Day 90] -Ventilator-free days [Time Frame: Day 28] -Intensive care unit-free days [Time Frame: Day 28] -Hospital-free days [Time Frame: Day 28]

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
		Patients or proxies who express their opposition to study participation			
NCT04446286 Bicentric Study on the Use of ECMO-VV or VA for Severe ARDS Associated With Covid-19 (ECMO-SL-CoV-2) Pierre-Emmanuel FALCOZ Recruiting August 18, 2020	Observational, case series	(France) (N= 50 participants) Inclusion Criteria: Patient over the age of 18; Diagnostic COVID-19 by RT-PCR; Hospitalisation in resuscitation for the management of complications related to COVID-19 Implanted ECMO-VV or VA during hospitalisation; Patient agreeing to participate in the study Exclusion Criteria: Subject who has expressed opposition to participating in the study. Subject under guardianship or trusteeship Subject under safeguard of justice	ECMO Implantation	None	-Retrospective description of effect of the ECMO-VV or ECMO-VA in the management of severe ARDS refractory in patients of the Strasbourg and Louvain centres with covid-19 [Time Frame: files analysed retrospectively from March 1st, 2020 to August 1st, 2020 will be examined]
NCT04366921 European/Euro-ELSO Survey on Adult and Neonatal/ Pediatric COVID-19 Patients in ECMO (EuroECMO-COVID) Roberto Lorusso Recruiting April 2021	Observational, prospective cohort	(Netherlands) (N= 150 participants) Inclusion Criteria: -Laboratory-confirmed COVID-19 infection by real-time PCR (polymerase chain reaction) -ECMO for treatment severe lung disease COVID-19 related Exclusion Criteria: Patients treated with ECMO for other concomitant causes.	ECMO	None	-Age [Time Frame: at baseline] -Gender [Time Frame: at baseline] -Weight [Time Frame: at baseline] -Height [Time Frame: at baseline] -BMI [Time Frame: at baseline] -Pre-existing pulmonary disease y/n [Time Frame: at baseline] -Main co-morbidities y/n [Time Frame: at baseline] -Date of signs of COVID-19 infection [Time Frame: at baseline or date of occurence] -Date of positive swab [Time Frame: at baseline or date of occurence]

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
					-Pre-ECMO length of hospital stay [Time Frame: at or during ECMO-implant] -Pre-ECMO length of ICU stay [Time Frame: at or during ECMO-implant] -Pre-ECMO length of mechanical ventilation days [Time Frame: at or during ECMO-implant] -Use of antibiotics [Time Frame: up to 6 months] -Use of anti-viral treatment [Time Frame: up to 6 months] -Use of second line treatment [Time Frame: up to 6 months] -Indications for ECMO-implant [Time Frame: at ECMO-implant] respiratory or cardiac -Type of ECMO-implant [Time Frame: at ECMO-implant] -Type of access [Time Frame: at ECMO-implant] -Date of ECMO implant [Time Frame: at ECMO-implant] -ECMO blood flow rate [Time Frame: from day of ECMO-implant for every 24 hours until date of weaning or death, up to 6 months] -ECMO gas flow rate [Time Frame: from day of ECMO-implant for every 24 hours until date of weaning or death, up to 6 months] -ECMO configuration change [Time Frame: up to 6 months] -Date of ECMO configuration change [Time Frame: up to 6 months] -New ECMO configuration [Time Frame: up to 6 months]

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
					-Indications for ECMO configuration change [Time Frame: up to 6 months] -Ventilator setting on ECMO [Time Frame: from day of ECMO-implant for every 24 hours until date of weaning or death, up to 6 months] -Anticoagulation during ECMO [Time Frame: from day of ECMO-implant for every 24 hours until date of weaning or death, up to 6 months] -Frequency of ECMO circuit change [Time Frame: up to 6 months] -ECMO complications [Time Frame: up to 6 months] -ECMO Weaning [Time Frame: from day of ECMO-implant for every 24 hours until date of weaning or death, up to 6 months] -ICU discharge [Time Frame: from day of ICU-admission for every 24 hours until date of discharge or death, up to 6 months] -Main cause of death [Time Frame: 6 months] -Type of discharge [Time Frame: up to 6 months] -Alive/deceased [Time Frame: 6 months]
NCT04383678 Outcome of COVID-19 Patients After Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome	Observational Retrospective Cohort	(Finland) (N= 200 participants) Inclusion Criteria: PCR-confirmed or suspected COVID-19 infection with ARDS who require any ECMO therapy, Child, Older Child, and Adult	Device: Extracorporeal membrane oxygenation Veno-venous or veno-arterial extracorporeal oxygenation	None	In-hospital mortality [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Death on ECMO [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation]

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
Fausto Biancari Recruiting December 31, 2020		Exclusion Criteria: None			-Stroke [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Blood stream infection [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Lung complications requiring surgical treatment [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Blood transfusion [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Acute kidney injury [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Duration of mechanical ventilation [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Deep vein thrombosis [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Pulmonary embolism [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Length of ICU stay [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Length of hospital stay [Time Frame: During index hospital stay follow-up until 1 year after ECMO initiation] -Death after hospital discharge [Time Frame: During index hospital

Study ID & Title (Author, Year) Status Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
					stay follow-up until 1 year after ECMO initiation]
NCT04340414 Safety and Effectiveness of Low-flow ECMO Driving by CVVH Machine in Severe NCP Yun Long Recruiting October 15, 2020	Interventional, Single group assignment	(China) (N=14) Inclusion Criteria: 1. NCP with severe acute respiratory distress syndrome with ratio of partial pressure of arterial oxygen over fraction of inspired oxygen (PaO2:FiO2)<150 and PEEP >10cmH2O 2. Driving pressure> 20cmH2O 3. RR>30bpm 4.PaCO2>55cmH2O and/or PH>7.3 Exclusion Criteria: 1. poor venous vascular condition and unavailable for central venous catheter placement Aged 14 years and older	Device: Low flow ECMO driving by CVVH machine With aim to clear CO2 and improve oxygenation, a low flow ECMO treatment (using oxygenator membrane of kid type) driving by CVVH machine will be performed in the NCP with severe ARDS	None	-PaCO2 [Time Frame: Day 1] -Driving Pressure [Time Frame: Day 1] -Tidal volume [Time Frame: Day 1]
NCT04343404 Place of ECMO in the Management of Severe Refractory ARDS Associated With Covid-19 (ECMO-COVID-19) Pierre-Emmanuel FALCOZ Completed April 15, 2020	Observational Case-Only, Retrospective	(France) (N=100 participants) Inclusion Criteria: Patient over the age of 18; Diagnostic COVID-19 by RT-PCR; Hospitalisation in resuscitation for the management of complications related to COVID-19 Implanted ECMO-VV during hospitalisation; Patient agreeing to participate in the study Exclusion Criteria: Subject under guardianship or trusteeship Subject under safeguard of justice	ECMO	None	Retrospective description of COVID-19 patients receiving respiratory ECMO-VV supplementation and what happens to them [Time Frame: Files analysed retrospectily from March 1st, 2020 to April 15, 2020 will be examined]

Appendix E. Critical Appraisal of Included Studies

CRITICAL APPRAISAL
Role of extracorporeal membrane oxygenation in COVID-19: A systematic review
Haiduc, et al., 2020

Role of extracorporeal membrane oxygenation in COVID-19: A systematic review (Haiduc, 2020)
Link: https://onlinelibrary.wiley.com/doi/full/10.1111/jocs.14879

General Information

Date form completed *(dd/mm/yyyy)*	First draft: 8/12/ 2020 Agreement: 8/14/ 2020 Final copy: 8/17/ 2020
Name of person extracting data	Encarnacion, PJC and Obmana, SML
Reference citation	Haiduc AA, Alom S, Melamed N, Harky A. Role of extracorporeal membrane oxygenation in COVID-19: A systematic review. J Card Surg. 2020;1–9. https://doi.org/10.1111/jocs.14879
Year of publication	2020
Language	☐ English. ☐ Non-English, specify____

Notes:
Approved research question:

Would Extracorporeal Membrane Oxygenation (ECMO) significantly improve the survival rate of critically ill COVID-19 patients with severe respiratory failure as compared to those in mechanical ventilation?

P – ARDS with or without COVID-19, all age groups
I – ECMO, either VA or VV, with or without supportive therapies
C – Mechanical ventilation alone
O – Survival, Hospitalization days, Resolution of symptoms
S – Systematic Reviews

Study Characteristics

Population	Patients with COVID-19
Intervention	ECMO
Comparator	Not specified
Outcomes	Mortality rate
Study design of included studies	Case reports/series, retrospective cohort studies, cross-sectional studies, retrospective case control studies
Does the study answer your research questions/s:	Yes

Appraisal Result		
Item	Result	
1	No	
2*	No	
3	Yes	
4*	No	
5	Yes	
6	No	
7*	No	Overall rating: **Critically Low** There is more than one critical weakness especially in domain numbers 2, 4, 7, and 13. Moreover, there are 5 non-critical weaknesses in the study
8	Yes	
9*	Includes only NRSI Partial Yes	
10	No	
11*	No meta-analysis done	
12	No meta-analysis done	
13*	No	
14	No	
15*	No meta-analysis done	
16	No	

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	Did the research questions and inclusion criteria for the review include the components of PICO?	"The overall mortality rate following the collation of the data from the 25 articles selected in this review was 19.83%." *Page 2* "This study aims to investigate the current literature and explore the effectiveness of ECMO on patients with COVID-19." *Page 2* The main exclusion criteria were narrative reviews, consensus documents, editorials and commentaries without reporting on patient data or outcomes. Studies were included if they contained primary data on patients who were diagnosed with COVID-19 and were subsequently put on ECMO. *Page 2*	☐ For Yes (ALL the following): Population Intervention Comparator group Outcome Timeframe for follow-up - Optional (Recommended) ☐ No
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No information	☐For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: review question(s) a search strategy inclusion/exclusion criteria a risk of bias assessment ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, *and* a plan for investigating causes of heterogeneity justification for any deviations from the protocol ☐ No
3	Did the review authors explain their selection of	"The main exclusion criteria were narrative reviews, consensus document, editorials and commentaries without reporting on patient data or	☐ For Yes, the review should satisfy ONE of the following: *Explanation for* including only RCTs OR *Explanation for* including only NRSI

	the study designs for inclusion in the review?	outcomes. Studies were included if they contained primary data on patients who were diagnosed with COVID-19 and were subsequently put on ECMO." *Page 2*	OR *Explanation for* including both RCTs and NRSI ☐ No
4	Did the review authors use a comprehensive literature search strategy?	A comprehensive literature search was conducted using Global Health, EMBASE, Medline, and Cochrane databases to identify articles pertaining to ECMO and COVID-19. The "Preferred Reporting Items for Systematic Reviews and Meta-analysis" (PRISMA) guidelines were adhered to. The search strategy was split into following two categories: (a) COVID-19 and (b) ECMO. Keywords and MeSH terms relating to these categories were used to optimize the output from the database search including "Coronavirus" OR "nCoV*" OR "2019-nCoV" OR "COVID*" OR "SARS-CoV*" AND "ECMO" OR "VV-ECMO" OR "VA-ECMO" OR "Extracorporeal membrane oxygenation." All the relevant articles were screened and selected for inclusion by two authors and any disagreements were resolved through consensus and vote. *Page 2*	☐For Partial Yes (all the following): searched at least 2 databases (relevant to research question) provided key word and/or search strategy justified publication restrictions ☐For Yes, should also have (all the following): searched the reference lists / bibliographies of included studies searched trial/study registries included/consulted content experts in the field where relevant, searched for grey literature conducted search within 24 months of completion of the review ☐ No
5	Did the review authors perform study selection in duplicate?	"All the relevant articles were screened and selected for inclusion by two authors and any disagreements were resolved through consensus and vote." *page 2, paragraph 4*	☐For Yes, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐ No
6	Did the review authors perform data extraction in duplicate?	Data extracted from the included articles were tabulated, and then, a narrative synthesis was undertaken to identify key themes in the literature. *Page 2*	☐For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

			☐ No
7	Did the review authors provide a list of excluded studies and justify the exclusions?	No information	☐ For Partial Yes: provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: Justified the exclusion from the review of each potentially relevant study ☐ No
8	Did the review authors describe the included studies in adequate detail?	Entire page 3, 4, and 5	☐ For Partial Yes (ALL the following): described populations described interventions described comparators described outcomes described research designs ☐ For Yes, should also have ALL the following: described population in detail described intervention in detail (including doses where relevant) described comparator in detail (including doses where relevant) described study's setting timeframe for follow-up ☐ No
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		RCTs ☐For Partial Yes, must have assessed RoB from unconcealed allocation, *and* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) ☐For Yes, must also have assessed RoB from: allocation sequence that was not truly random, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No

			☐ Includes only NRSI
		A quality assessment for all the included articles was undertaken, using the NIH quality assessment tool for the appropriate studies. No articles were excluded based on their quality score." *Page 2*	NRSI ☐For Partial Yes, must have assessed RoB: from confounding, *and* from selection bias ☐For Yes, must also have assessed RoB: methods used to ascertain exposures and outcomes, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only RCTs
10	Did the review authors report on the sources of funding for the studies included in the review?		☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies ☐No
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Not applicable	RCTs ☐For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. AND investigated the causes of any heterogeneity ☐ No ☐No meta-analysis done
		Not applicable	For NRSI ☐ For Yes:

			The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta-analysis done
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not applicable	☐For Yes: included only low risk of bias RCTs OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. ☐No ☐No meta-analysis done
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	A quality assessment for all the included articles was undertaken, using the NIH quality assessment tool for the appropriate studies. No articles were excluded based on their quality score." *Page 2*	☐ For Yes: included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ☐ No
14	Did the review authors provide a satisfactory	No information	☐For Yes: There was no significant heterogeneity in the results

	explanation for, and discussion of, any heterogeneity observed in the results of the review?		OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ☐ No
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not applicable	☐For Yes: performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐No ☐No meta analysis conducted
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No information	☐For Yes: The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest ☐ No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ*. 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ*. 2017;(358).

CRITICAL APPRAISAL
Extracorporeal Life Support: The Next Step in Moderate to Severe ARDS—A Review and Meta-Analysis of the Literature
Aretha, et al., 2019

Extracorporeal Life Support: The Next Step in Moderate to Severe ARDS—A Review and Meta-Analysis of the Literature (Aretha, et al., 2019)
Link: http://downloads.hindawi.com/journals/bmri/2019/1035730.pdf

General Information

Date form completed *(dd/mm/yyyy)*	First draft: 8/12 Agreement: 8/14 Final copy: 8/17
Name of person extracting data	Encarnacion, PJC and Obmana, SML
Reference citation	Aretha, D., Fligou, F., Kiekkas, P., Karamouzos, V., & Voyagis, G. (2019). Extracorporeal Life Support: The Next Step in Moderate to Severe ARDS - A Review and Meta-Analysis of the Literature. BioMed Research International, 2019. https://doi.org/10.1155/2019/1035730
Year of publication	2019
Language	☐ English. ☐ Non-English, specify____
Notes: Approved research question: Would Extracorporeal Membrane Oxygenation (ECMO) significantly improve the survival rate of critically ill COVID-19 patients with severe respiratory failure as compared to those in mechanical ventilation? P – ARDS with or without COVID-19, all age groups I – ECMO, either VA or VV, with or without supportive therapies C – Mechanical ventilation alone O – Survival, Hospitalization days, Resolution of symptoms S – Systematic Review	

Study Characteristics

Population	patients with moderate to severe ARDS
Intervention	ECMO and $ECCO_2R$
Comparator	Conventional mechanical ventilation
Outcomes	Hospital mortality; or, ICU mortality; or, 6-month mortality
Study design of included studies	RCTs, quasi-RCTs, observational studies, upcoming RCTs
Does the study answer your research questions/s:	Yes

Appraisal Results		
Item	Result	
1	No	
2*	No	
3	Yes	
4*	No	
5	Yes	
6	No	
7*	No	
8	Yes	
9*	RCT - Yes NRSI - No	
10	No	
11*	RCT – No NRSI – No	
12	Yes	
13*	Yes	
14	No	
15*	Yes	
16	Yes	

Overall rating:

Critically Low

There is more than one critical weakness especially in domain numbers 2, 4, 7, 9, and 11. Moreover, there are 4 non-critical weaknesses in the study

**Critical domains*

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	Did the research questions and inclusion criteria for the review include the components of PICO?	In this review, we focus on the most important clinical trials to unveil a final conclusion about the effectiveness of ECMO and ECCO2R in moderate to severe ARDS patients. *Page 1* Our main outcome of interest was hospital mortality, and if this was not provided, then we used ICU or 6-month mortality. *Page 2*	☐ For Yes (ALL the following): Population Intervention Comparator group Outcome Timeframe for follow-up - Optional (Recommended) ☐ No
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No information	☐For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: review question(s) a search strategy inclusion/exclusion criteria a risk of bias assessment ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, *and* a plan for investigating causes of heterogeneity justification for any deviations from the protocol ☐ No
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Unfortunately, the evaluation of previous RCTs and observational trials has revealed major methodological issues. In this review, we focus on the most important clinical trials to unveil a final conclusion about the effectiveness of ECMO and $ECCO_2R$ in moderate to severe ARDS patients. *Page 1*	☐ For Yes, the review should satisfy ONE of the following: *Explanation for* including only RCTs OR *Explanation for* including only NRSI OR *Explanation for* including both RCTs and NRSI ☐ No
4	Did the review authors use a comprehensive	Two reviewers (DA and VK) systematically and independently searched for clinical studies by using combinations of the following search terms:	☐For Partial Yes (all the following): searched at least 2 databases (relevant to research question)

	literature search strategy?	"extracorporeal life support," "extracorporeal membrane oxygenation," "extracorporeal carbon dioxide removal," "hypoxemia," "acute respiratory distress syndrome," "mortality," and "outcome." The US National Library of Medicine (PubMed), Web of Science, Cochrane Library, and Excerpta Medical Database (EMBASE) were included in the search, which initially took place in the first week of September 2018 and then was updated with additional information in the second week of November 2018 and in the last week of May 2019. First, studies that were retrieved were screened according to their titles and abstracts. Only studies on humans and that had an English abstract were included for screening. Second, the full text of the selected articles was evaluated to make a final determination for inclusion. Finally, the reference lists of the eligible articles were checked for potentially relevant articles (not included in the first online searches). The full texts of these additional articles were also studied for eligibility and possible inclusion. Any discrepancies between the two reviewers were discussed with a third reviewer (FF) until a consensus had been achieved. Finally, 17 articles fulfilled the criteria of the review, while three more articles were retrieved from the reference list of relevant articles, which were then included in the final review as well (totaling 20). *Page 2* One international study is currently evaluating the ECCO2R technique, enabling ultra-LPV in ARDS patients. In the UK, the REST clinical trial (Clinical Trials.gov NCT02654327) is evaluating ARDS patients treated with lower tidal volume ventilation	provided key word and/or search strategy justified publication restrictions ☐For Yes, should also have (all the following): searched the reference lists / bibliographies of included studies searched trial/study registries included/consulted content experts in the field where relevant, searched for grey literature conducted search within 24 months of completion of the review ☐ No

		versus standard care and is including 1.120 patients with PaO2/FiO2 <150 mmHg. *Page 9*	
5	Did the review authors perform study selection in duplicate?	Two reviewers (DA and VK) systematically and independently searched for clinical studies by using combinations of the following search terms: "extracorporeal life support," "extracorporeal membrane oxygenation," "extracorporeal carbon dioxide removal," "hypoxemia," "acute respiratory distress syndrome," "mortality," and "outcome." *Page 2* Any discrepancies between the two reviewers were discussed with a third reviewer (FF) until a consensus had been achieved. *Page 2*	☐For Yes, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐ No
6	Did the review authors perform data extraction in duplicate?	No information	☐For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. ☐ No
7	Did the review authors provide a list of excluded studies and justify the exclusions?	No information	☐ For Partial Yes: provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: Justified the exclusion from the review of each potentially relevant study ☐ No
8	Did the review authors describe the included studies in adequate detail?	Most studies have important limitations regarding quality and design, with substantial qualitative heterogeneity among them. In the 20 included studies (2,956 patients), 1,185 patients received ECLS. Of them, 976 patients received ECMO and 209 patients received ECCO2R. When ECMO was	☐ For Partial Yes (ALL the following): described populations described interventions described comparators described outcomes described research designs

		used, the investigators mainly used VV-ECMO, but in a small number of patients, VA-ECMO was also used. Seven studies (428 ECMO patients) had mainly enrolled patients suffering from H1N1-associated ARDS, while one study (203 patients) enrolled immunocompromised patients. *Page 5* Quantitative Synthesis of the Study Findings. Hospital mortality was reported in 11 studies. Of them, 10 studies included in the pooled results (of 1,497 patients, 1,040 received ECLS). Putting the results of the two RCTs [9, 10], the two quasi-RCTs [11, 12], and the four prospective observational trials [13–16] together, ECMO failed to show any survival benefit in ARDS patients (Figure 2). Because PQ< 0.001 and I^2 = 83%, a RE model was used (RE OR = 0.96, 95% CI = 0.52–1.77). In the subgroup analysis, when restricted to RCTs [9, 10] and quasi-RCTs [11, 12], there was a mortality difference favouring the ECMO group (PQ = 0.33, I^2 = 12.2%, FE OR = 0.51, 95% CI = 0.37–0.70) (Figure 3). Furthermore, pooling the results of the two most important RCTs on this issue together [9, 10], the ECMO procedure does not favour severe ARDS patients (PQ< 0.001, I^2 = 92.7%, RE OR = 2.23, 95% CI = 0.18–28.07) *Page 5* *Entire pages 3 and 4*	☐ For Yes, should also have ALL the following: described population in detail described intervention in detail (including doses where relevant) described comparator in detail (including doses where relevant) described study's setting timeframe for follow-up ☐ No
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies	The bias level was estimated using the Cochrane Collaboration risk-of-bias instrument. *Page 5*	RCTs ☐For Partial Yes, must have assessed RoB from unconcealed allocation, *and* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) ☐For Yes, must also have assessed RoB from: allocation sequence that was not truly random, *and*

	that were included in the review?		selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only NRSI
		No information	NRSI ☐For Partial Yes, must have assessed RoB: from confounding, *and* from selection bias ☐For Yes, must also have assessed RoB: methods used to ascertain exposures and outcomes, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only RCTs
10	Did the review authors report on the sources of funding for the studies included in the review?	No information	☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies ☐No
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Dichotomous outcomes were reported using odds ratios (ORs) and their 95% confidence intervals (CIs). Heterogeneity among the studies was determined by calculating the Q and the I^2 statistic. For the Q statistics, a P value <0.05 was selected for high heterogeneity, while for the I statistics, heterogeneity was classified as being high when greater than 75%, moderate when between 50% and 74%, and low when less than 25%. In the presence of low heterogeneity (PQ< 0.05, I^2< 25%), a fixed-effects (FE) model was used, while in the	RCTs ☐For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. AND investigated the causes of any heterogeneity ☐ No

		case of moderate or high heterogeneity, a random-effects (RE) model was used. To assess publication bias, funnel plots (treatment difference vs. study precision) and a linear regression analysis (Egger's test) were used.)e data analysis was conducted using the Meta-Essentials tool for meta-analysis [23] and SPSS version 22 (IBM SPSS Statistics for Mac, Armonk, NY, USA). *Page 2* Quantitative Synthesis of the Study Findings. Hospital mortality was reported in 11 studies. Of them, 10 studies included in the pooled results (of 1,497 patients, 1,040 received ECLS). Putting the results of the two RCTs [9, 10], the two quasi-RCTs [11, 12], and the four prospective observational trials [13–16] together, ECMO failed to show any survival benefit in ARDS patients (Figure 2). Because PQ< 0.001 and I^2 = 83%, a RE model was used (RE OR = 0.96, 95% CI = 0.52–1.77). In the subgroup analysis, when restricted to RCTs [9, 10] and quasi-RCTs [11, 12], there was a mortality difference favouring the ECMO group (PQ = 0.33, I^2 = 12.2%, FE OR = 0.51, 95% CI = 0.37–0.70) (Figure 3). Furthermore, pooling the results of the two most important RCTs on this issue together [9, 10], the ECMO procedure does not favour severe ARDS patients (PQ< 0.001, I^2 = 92.7%, RE OR = 2.23, 95% CI = 0.18–28.07) *Page 5*	☐No meta-analysis done
		Quantitative Synthesis of the Study Findings. Hospital mortality was reported in 11 studies. Of them, 10 studies included in the pooled results (of 1,497 patients, 1,040 received ECLS). Putting the results of the two RCTs [9, 10], the two quasi-RCTs [11, 12], and the four prospective observational trials [13–16] together, ECMO failed to show any survival benefit in ARDS patients (Figure 2).	For NRSI ☐ For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present

		Because PQ< 0.001 and I^2 = 83%, a RE model was used (RE OR = 0.96, 95% CI = 0.52–1.77). In the subgroup analysis, when restricted to RCTs [9, 10] and quasi-RCTs [11, 12], there was a mortality difference favouring the ECMO group (PQ = 0.33, I^2 = 12.2%, FE OR = 0.51, 95% CI = 0.37–0.70) (Figure 3). Furthermore, pooling the results of the two most important RCTs on this issue together [9, 10], the ECMO procedure does not favour severe ARDS patients (PQ< 0.001, I^2 = 92.7%, RE OR = 2.23, 95% CI = 0.18–28.07) *Page 5*	AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta analysis done
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Our study has important limitations. First, we observed a high heterogeneity in our results, which was expected considering the changes in critical care practices, differences in design, inclusion criteria, and ECLS technologies over time. Our purpose, however, was to incorporate the entire body of evidence. Second, quantitative results are drawn from a limited number of studies, almost half of all the considered ones in the review, which does not allow for confidence in the consistency of the results. *Page 7 and 9*	☐For Yes: included only low risk of bias RCTs OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. ☐No ☐No meta analysis done
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Our review and meta-analysis of 20 studies including 2,956 patients revealed no significant differences in mortality in patients with ARDS treated with ECLS. However, when limited to higher quality studies, ECMO reduced in-hospital mortality when compared with conventional mechanical ventilation techniques. *Page 5*	☐ For Yes: included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ☐ No
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity	Generally, there was a significant level of heterogeneity across the clinical trials, which made it risky to pool the data into a meta-analysis." *Page 5*	☐For Yes: There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

	observed in the results of the review?	Our study has important limitations. First, we observed a high heterogeneity in our results, which was expected considering the changes in critical care practices, differences in design, inclusion criteria, and ECLS technologies over time. Our purpose, however, was to incorporate the entire body of evidence. Second, quantitative results are drawn from a limited number of studies, almost half of all the considered ones in the review, which does not allow for confidence in the consistency of the results. *Page 7 and 9* According to our results, ECLS use was not associated with a benefit in mortality rate in patients with ARDS. However, when restricted to higher quality studies, ECMO was associated with a significant benefit in mortality rate. Furthermore, in patients with H1N1, a potential benefit of ECLS was apparent. The current study highlights the significant heterogeneity among the studies and the limited number of high-quality data. *Page 9*	☐ No
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	The study distribution was relatively symmetrical on both sides of the mean; thus, concerns for publication bias were not raised, while no significant small study effects were indicated by Egger's test (P = 0.33). *Page 5*	☐For Yes: performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐No ☐No meta analysis conducted
16	Did the review authors report any	The authors declare that they have no conflicts of interest.	☐For Yes: The authors reported no competing interests OR

	potential sources of conflict of interest, including any funding they received for conducting the review?	*Page 9*	The authors described their funding sources and how they managed potential conflicts of interest ☐ No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ*. 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ*. 2017;(358).

Extracorporeal Membrane Oxygenation for Patients with COVID-19 in Severe Respiratory Failure

Mustafa, A., Alexander, P., Joshi, D., Tabachnick, D., Pappas, P., Tatooles, A. (2020)

Critical Appraisal

Reference: Mustafa, A. K., Alexander, P. J., Joshi, D. J., Tabachnick, D. R., Cross, C. A., Pappas, P. S., & Tatooles, A. J. (2020). Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure. JAMA Surgery. https://doi.org/10.1001/jamasurg.2020.3950

DIRECTNESS

Research Question	
P	**COVID-19 Patients with ARDS** "Patients with COVID-19 whose condition has rendered mechanical ventilatory support insufficient." *Page 1, paragraph 1*
I	**VV Extracorporeal Membrane Oxygenation (ECMO)** "We present our experience in using single-access, dual-stage venovenous ECMO" *Page 1, paragraph 1*
C	**No comparator.**
O	**Primary outcome: Survival** **Secondary outcome: Time to decannulation, hospitalization** "The primary outcome was survival following safe discontinuation of ventilatory and ECMO supports." *Page 1, paragraph 2*

APPRAISAL OF VALIDITY

1. Were the questions randomly assigned to treatment groups? (Randomization)

   No.

   Since the study is a retrospective case series and there was no comparator group, subjects were not randomized but their data were merely collected to determine the treatment effect.

   "Data were collected retrospectively from 40 consecutive patients with COVID-19 who were in severe respiratory failure and supported with ECMO."
   Page 1 Paragraph 2

2. Was allocation concealed? (Allocation Concealment)

   No.

   Since the study is a retrospective case series and there was no comparator group, subjects received the same treatment, therefore there was no need for allocation concealment.

   "Data were collected retrospectively from 40 consecutive patients with COVID-19 who were in severe respiratory failure and supported with ECMO."
   Page 1 Paragraph 2

3. Were baseline characteristics similar at the start of the trial?
No.
Since the study is a retrospective case series and there was no comparator group, subjects received the same treatment, therefore there was no need to determine whether subjects had similar baseline characteristics. A description of the baseline characteristics was provide instead.

"Care with ECMO was performed in 40 consecutive patients between the ages of 22 and 64 years (mean [SE] age, 48.4 [1.5] years); 30 (75%) were men, 16 (40%) were African American individuals, and 14 (35%) were Hispanic individuals (Table). The mean (SE) body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was 34.2 (1.1). Obesity was the primary preexisting condition (28 patients [70%]). All patients reached maximum ventilator support, with 90% placed in a prone position (29 patients [73%]), paralyzed (31 patients [78%]), or both, pre-ECMO; 24 patients (60%) required vasopressors. Eleven patients could not be placed in a prone position because of increasing hemodynamic instability and/or worsening oxygenation or ventilation with pronation. All patients demonstrated considerably elevated levels of inflammatory markers, such as D-dimer and ferritin, prior to ECMO use."
Page 1, Paragraph 3

4. Were patients blinded to treatment assignment?
No.
Since the study is a retrospective case series and there was no comparator group, subjects received the same treatment, therefore there was no need for blinding.

"Data were collected retrospectively from 40 consecutive patients with COVID-19 who were in severe respiratory failure and supported with ECMO."
Page 1 Paragraph 2

5. Were caregivers blinded to treatment assignments?
No.
Since the study is a retrospective case series and there was no comparator group, subjects received the same treatment, therefore there was no need for blinding.

"Data were collected retrospectively from 40 consecutive patients with COVID-19 who were in severe respiratory failure and supported with ECMO."
Page 1 Paragraph 2

6. Were outcome assessors blinded to treatment assignment?
Not mentioned.

7. Were all patients analysed in the groups to which they were originally randomized?
No.
Since the study is a retrospective case series and there was no comparator group, subjects were not randomized; instead, their data were merely collected to determine the treatment effect.

8. Was follow-up rate adequate?

Yes.

Since the case series is retrospective in nature, it is ensured that all subjects are accounted for with their outcomes noted.

APPRAISING THE RESULTS

1. How large is the effect treatment?

The effect size cannot be estimated as there is no comparator in the study. Presented below are the data from the study.

Outcome	population	no. of patients with the outcome	Measure
Mortality	40	6	15% (mortality rate)
Hospital Stay	40	29	44.5 (95% CI: 40.37-48.63) days (mean)

2. How precise is the estimate of the treatment effect?

The estimate of the treatment effect cannot be assessed for precision as there is no comparator in the study.

APPLICABILITY

The study, with a subject population of predominantly African Americans and none of Asian descent, limits its applicability to the Filipino population. Moreover, the study had predominantly male subjects which also limits the generalizability of its findings.

CONCLUSION

Overall, it can be concluded that the study has a low internal validity. This is due to the inherent limitation of the study design which does not have a comparator arm, nor randomization and blinding. Further, the applicability of the results may be limited due to the specific predominant characteristics of subjects in the study population.