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

Evidence Summary

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Service Line	Evidence Summary
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1. General information of the proposed health technology

Generic Name	Extracorporeal Machine Oxygenation (ECMO)
Product Name	Not applicable
Food and Drug Administration approved indication	Not applicable
Proposed Indication/s	Not applicable
Dosage Formulation/Strength	Not applicable
Route of Administration	Not applicable
Dosage Regimen	Not applicable
Therapeutic Class	Not applicable

2. Background

The World Health Organization (WHO) declared the novel coronavirus disease (COVID-19), caused by severe acute coronavirus 2 (SARS-COV-2), a global pandemic. The most common symptoms are fever, sore throat, malaise and dry cough. The symptoms are usually mild and begin gradually. It can spread from person-to-person through small droplets when coughing or sneezing. As of 06 September 2020, it has affected more than 213 countries and regions with at least 26, 763, 217 cases and 876, 616 deaths worldwide (WHO, 2020). Locally, there are over 48, 803 active cases and 3, 875 deaths.

Currently, there are no known treatments for COVID-19. As one of the multiple responses to this pandemic, the Philippine Health Insurance Corporation (PhilHealth), the national social health insurance of the Philippines, plans to cover the use of ECMO in COVID-19 patients with ARDS. They subsequently submitted a request to HTAC to review the safety, effectiveness, and potential resource requirements in the use of ECMO. 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 health technology assessment (HTA) review recommendations from selected countries and synthesize existing literature on the use of ECMO in both COVID-19 and non-COVID-19 patients.

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 COVDID-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. Responsiveness to disease magnitude, severity, and equity

3.1. Responsiveness to disease magnitude and severity

As of September 6, 2020, the Philippines has 237, 265 total cases of COVID-19. From the total cases, there are 48, 803 active cases with 683 (1.4% of active) severe cases, and 976 (2% of active) critical cases (DOH, 2020). A critical patient is defined as a patient with impending or ongoing respiratory failure, in need of mechanical ventilation, or with evidence of end-organ damage.

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, oxygenation and ventilatory interventions based on the treatment guideline for COVID-19 developed by the Philippine Society for Microbiology and Infectious Diseases. The guideline also states that if invasive mechanical ventilation fails to provide adequate oxygenation and ventilation, then extracorporeal membrane oxygenation (ECMO) is recommended (PSMID, July 2020).

4. Safety and effectiveness

4.1. 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 lung protective ventilation strategy 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. Additionally, the UK-NHS has set eligibility criteria for the use of ECMO in COVID-19 patients with ARDS. This is to assist clinicians in determining and prioritizing patients who will have improved outcomes with the use of ECMO.

Country/ Organization	UK- NHS (updated June 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*

None of the reviewed countries explicitly stated a strong recommendation for or against the use of ECMO in COVID-19 patients with ARDS

4.2. 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.

4.3 Evidence on Clinical Efficacy/Effectiveness and Safety

All three completed studies focused on ECMO as an intervention, with the systematic review (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 alone. 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 three studies included, pooling of outcomes was not performed.

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.

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 did not show statistically significant improvement in the mortality rates [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

Evidence among covid-19 patients 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.

Evidence among non-covid-19 patients It was not reported in the review from Aretha et al.

Duration of ECMO treatment

Evidence among covid-19 patients 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.

Evidence among non-covid-19 patients no reports from Aretha et al.

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 The incidence of adverse events was not reported 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 increased among patients who used ECMO [OR: 2.38, 95% CI (0.84, 6.75)] (two RCTs, two quasi-RCTs, two observational studies), however

the result was not statistically significant. The results were based on pooling different study designs. A study which evaluated a different intervention ($ECCO_2R$) was also included in the pooling for this outcome.

4.6. Risk of bias assessment

Based on the risk of bias assessment of the two SRs, Haiduc, et al. did not report the individual risk-of-bias (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. Moreover, it should be noted that non-randomized clinical trials included in Aretha et al. have inherent high risk of bias as they are actually observational studies.

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.

5. Household financial impact

Evidence not reviewed.

6. Cost-effectiveness

Evidence not reviewed.

7. Affordability and viability

Resource Requirements

Nationwide, eight (8) hospitals have ECMO machines, four of which are public and four are private hospitals. There are only 13 ECMO machines in the country, with 12 ECMO in Metro Manila and one in Davao City. The use of ECMO would need a fully equipped intensive care unit (ICU), with a negative pressure ventilation if it shall be used for COVID-19 patients. Each patient under ECMO will need 4 specialist doctors and 4 allied health staff per shift (3 shifts per day). There is a daily need for multiple units of different blood products.

According to the previous hospitalization data on non-COVID-19 patients from the National Kidney Institute from June to March 2020 (n=21), the use of ECMO in leptospirosis patients with severe ARDS will incur an average an Php 4,082,472.68 for 11 days of ECMO use per patient. Further, the acquisition cost of each ECMO machine is around Php 8 to 10 million based on the submitted data from the DOH – Health Facilities Development Bureau (HFDB).

8. Recommendation

At the moment, there is **insufficient evidence to recommend use of ECMO on patients with COVID-19** in terms of decreasing mortality rate, decreasing hospitalization stay and resolution of symptoms. Moreover, the use of ECMO may increase the risk of bleeding; although this is an indirect evidence from ARDS-related studies before the COVID-19 pandemic.

Furthermore, the use of ECMO generally demands many resources in terms of:

- Personnel
  TCVS, anesthesiologists, pulmonologist, intensivists, pathologists, rehabilitation physician, ICU nurses, respiratory therapist and laboratory technician, and other allied health personnel
- Equipment
  Procurement and maintenance cost of the following machines: ECMO machine, telemetry, mechanical ventilator
- Infrastructure
  Adapting to general spatial requirements of ECMO and COVID-19 infection prevention and control (IPC) measures: negative pressure room, HEPA filters, and separate ward
- Supplies
  Blood products and PPEs for personnel
- Training cost for ECMO cannulation, and maintenance.

This is an interim recommendation based on existing evidence and may change based on the results of on-going and future studies on the use of ECMO on COVID-19.

9. References

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