Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19-associated acute respiratory distress syndrome patients, should extracorporeal membrane oxygenation be used?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected adult COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO or NHS England criteria. **after careful consideration of cost, resources, expertise available*	Very low	Weak
We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected pediatric COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO criteria. **after careful consideration of cost, resources, expertise available*	Very low	Weak

Consensus Panel Issues

A suggestion to offer ECMO is given after consideration of the perceived benefits from the available evidence and limitations posed by the intervention. The panel recognizes the cost, resources, and expertise needed to place a patient on ECMO. Sustainability or capacity to maintain on ECMO is likewise important since once ECMO is initiated, it would be difficult to simply withdraw treatment when resources or financial capability is depleted.

KEY FINDINGS

- We reviewed 10 cohort studies which determined the effects of extracorporeal membrane oxygenation (ECMO) among adult patients with COVID-19-associated acute respiratory distress syndrome. Overall, the use of ECMO significantly reduced all-cause mortality when compared with optimal ventilator strategy. In propensity-matched analysis, greater association between ECMO and reduction in mortality was observed. However, the use of ECMO was associated with longer duration of mechanical ventilation, duration of intensive care unit stay, and overall length of hospitalization. In terms of adverse events, the use of ECMO was associated with significant coagulopathy, gastrointestinal bleeding, intracranial hemorrhage, pneumothorax, and pulmonary embolism. Six out of 10 cohort studies were assessed to have high risk of bias due to issues of comparability of intervention and control groups while four out of 10 cohort studies were assessed to have low risk of bias. Overall certainty of evidence downgraded to very low due to risk of bias and inconsistency. All outcomes included in this review were in-hospital outcome measures.

- We reviewed 13 observational studies which described the effects of ECMO among children with COVID-19 ARDS. Overall, the mortality among children with COVID-19 ARDS who received ECMO was 23.08% by summation. However, the association was not statistically significant. Serious adverse events observed with the use of ECMO were acute kidney injury, cerebral hemorrhage, cerebral infarction, circuit thrombi, pneumothorax, pulmonary hemorrhage, gastrointestinal bleeding, pulmonary embolism, right atrial thrombosis, and seizures. Overall certainty of evidence was very low due to risk of bias and imprecision.

PREVIOUS RECOMMENDATION
As of 03 January 2022

We suggest the use of Extracorporeal Membrane Oxygenation (ECMO) for judiciously selected COVID-19 patients with severe Acute Respiratory Distress Syndrome (ARDS) based on the ELSO criteria.
(Very low certainty of evidence; Weak recommendation)

INTRODUCTION

In COVID-19 patients with acute respiratory distress syndrome (ARDS) or COVID-19 ARDS, severe hypoxemia complicated by respiratory failure may persist despite optimal mechanical ventilation strategies [1]. In the Philippines, COVID-19 ARDS was observed in about 10.9% [2] to 20.6% [3] of 2,115 adult COVID-19 patients admitted in two tertiary hospitals in Manila and Cebu contributing up to 42.9% of COVID-19-related mortality. Extracorporeal Membrane Oxygenation (ECMO) has been used for patients with acute severe cardiac or respiratory failure with high mortality risk. Initiation of ECMO in cases of COVID-19 ARDS refractory to optimal mechanical ventilation may lead to improvement in oxygenation through a homogeneous ultraprotective ventilation strategy [4]. Current practice takes into consideration referring patients with COVID-19 ARDS refractory to lung-protective ventilation for ECMO initiation. Latest guidance from Philippine COVID-19 Living Clinical Practice Guidelines suggested the use of ECMO for judiciously selected COVID-19 patients with ARDS based on very low certainty of evidence. This review aims to synthesize and update the current evidence on clinically important outcomes associated with the use of ECMO among adult and pediatric patients with COVID-19 ARDS.

REVIEW METHODS

A systematic literature search was conducted in PUBMED, Cochrane Library, clinicaltrials.gov databases on the use of ECMO in adult and pediatric patients with COVID-19 ARDS from inception to January 2023. The following keywords were used: (“extracorporeal membrane oxygenation” or “ECMO”) and (“COVID-19” or “COVID-19-associated acute respiratory distress syndrome” or “COVID-19 ARDS”). Our detailed search strategy and keywords used are presented in Appendix 2. No restrictions were applied as to the age of participants and publication language. Last date of search was 08 January 2023. The retrieved titles and abstracts were independently screened by two reviewers for inclusion. Studies which used ECMO among patients with COVID-19 ARDS compared with optimized ventilatory support (non-ECMO) were retrieved for full-text review. Eleven full-text articles (10 cohort studies and one systematic review and metaanalysis) were retrieved, critically appraised, and analyzed. The PRISMA Flow Diagram is shown in Appendix 3. The quality of the included studies were evaluated using the Newcastle-Ottawa Scale for Cohort Studies and the Assessment of Multiple Systematic Reviews (AMSTAR) tool. Critical appraisal of included studies is presented in Appendix 4 and 5. Critical outcomes identified for this review were COVID-19-related mortality and adverse events. Important outcomes included clinical improvement, clinical deterioration, and duration of mechanical ventilation. Outcomes with at least two studies were pooled in to a metaanalysis. Metaanalysis was performed in random-effects model with odds ratio as effect size estimate for dichotomous outcomes and difference in means (or mean difference) for continuous outcomes. Heterogeneity was estimated using I^2 statistic. A sensitivity analysis was planned according to study design (matched versus propensity-matched cohort studies), age, and other factors as necessary. Outcome-specific certainty of evidence was evaluated using the GRADE approach.

RESULTS

A. Use of ECMO in the Adult Patients with COVID-19 ARDS

Characteristics of included studies

We found 10 cohort studies [5-14] from Saudi Arabia [5], China [6,7,10], France [8], Germany [9], USA [11,12], Canada [13], and the United Kingdom [14] with 29,843 adult patients diagnosed with COVID-19 ARDS. A total of 2,692 patients who received ECMO (intervention group) was compared with 27,151 patients who received optimal ventilatory support (non-ECMO control group). Patients in the ECMO group was generally younger at 17 to 75 years old when compared to the non-ECMO group at 15 to 108 years old. In one study [11], patients aged >70 years were excluded for ECMO initiation. COVID-19 was diagnosed and confirmed using Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction (RT-PCR). ARDS was defined according to the Berlin definition [15]. Nine out of 10 studies adapted the Extracorporeal Life Support Organization (ELSO) guidelines on ECMO initiation [5-13] while one study [14] used the National Health Service (NHS) England indications for ECMO provisions [14]. Only five studies [6,7,10,11,14] listed specific contraindications for ECMO initiation. Indications [5-14] and specific contraindications [6,7,10,11] for ECMO initiation cited in the included studies are summarized in Table 1. Venovenous ECMO (VV-ECMO) was used in eight studies [5,7-11,13,14] (1,487 out of 2,692 patients, 55%) while two studies [6,12] (1,187 out of 2,692 patients, 44%) did not specify the type of ECMO used but ECMO initiation was mainly indicated for COVID-19 ARDS. In three studies [5,7,10] (n=16/2,692 patients, 1%), veno-arterial ECMO (VA-ECMO) was initiated for patients who underwent cardiac arrest and/or shock.

Table 1. Indications and Specific Contraindications for ECMO initiation

Indications for ECMO initiation based on ELSO guidelines and the NHS England Indications for ECMO Provisions
1. PaO_2:FiO_2 ratio <50mmHg for >3 hours and/or[5-14]
2. PaO_2:FiO_2 ratio <60-80mmHg for >6 hours and/or[5-14]
3. Blood pH <7.20 + $PaCO_2$ >60-80mmHg for >6-8 hours at a respiratory rate of 30-35 breaths per minute
4. PaO_2:FiO_2 ratio <100 at FiO_2 of 1.0[5-14]
5. Blood pH <7.20 despite optimization of mechanical ventilator[6]
6. Severe air leakage syndrome[6]
7. Potentially reversible severe respiratory failure (SRF) defined as severe hypoxemia, Murray Score >3, or uncompensated hypercapnia[14]
Specific Contraindications for ECMO Initiation[6,7,10,11,14]
1. Advanced age[6] or age >70 years old[11]
2. Blood pH of ≤6.9 or lactate ≥14.0 mmol/L[11]
3. Cardiac arrest without return of spontaneous circulation[11]
4. Complicated with irreversible disease[6,7] or severe organ failure[14]
5. Contraindications of anticoagulation[6,7,11]
6. Do Not Intubate or Do Not Resuscitate status[11]
7. Immunosuppression defined as absolute neutrophil count <400/mm^3[6,10] or immunocompromised status[7]
8. Mechanical ventilation lasted for more than 7 days at higher ventilator settings defined as FiO_1>0.90 and plateau pressure>30cmH_2O[6,7,10]
9. Multisystem organ failure involving three or more organ systems[11]
10. Non-recoverable comorbidity such as major central nervous system damage or terminal malignancy[10], permanent immobility in active malignancy[11] or severe symptomatic chronic organ failure such as cirrhosis, end-stage renal disease on dialysis, end-stage cardiomyopathy, severe chronic lung disease[11]
11. Projected life expectancy ≤5 years prior to SARS-CoV-2 infection[11]
12. Recent or expanding central nervous system hemorrhage[10,11]
13. Refusal to receive blood transfusion[11]
14. Significant frailty[14]
15. Vascular anatomical malformations or lesions in the puncture site[6,7]

Optimal ventilatory support was employed with the following settings: fraction of inspired oxygen (FiO_2) ≥0.80, tidal volume of 6mL/kg ideal body weight, and positive end-expiratory pressure (PEEP) ≥10cmH_2O. Optimal ventilatory support was used in the ECMO group prior to ECMO initiation and to the non-ECMO as

control group. Standard of care for COVID-19 ARDS across the 10 studies varied according to prevailing local and international guidelines. Outcomes measured included all-cause mortality at 30-60 days of follow-up period [5-14], serious adverse events (SAE) or complications [5,6,9-11], duration of mechanical ventilation [5,7,9], length of intensive care unit admission [5,6,9], overall length of hospital stay [5-7,12], and time-to-negative SARS-CoV-2 RT-PCR [5]. Characteristics of included studies is presented in Appendix 6.

Efficacy outcomes

Based on 10 cohort studies [5-14], the use of ECMO was associated with significant reduction in all-cause mortality (OR 0.64, 95% CI 0.41-0.99; I^2=94%; very low certainty). Out of 10 cohort studies, three studies [7,11,14] performed propensity-score matching between ECMO and non-ECMO groups. These propensity-matched cohort studies further excluded moribund patients defined as patients who died within 24 hours after ECMO initiation [7], severe organ dysfunction or multi-organ failure [11], and clinician's perceived futility [14]. In the propensity-score matched analysis, greater reduction in all-cause mortality was observed in the ECMO group (OR 0.23, 95% CI 0.10-0.52; I^2=82%; low certainty) when compared to non-ECMO group.

Even though ECMO was associated with lower mortality, significantly longer duration of mechanical ventilation (MD +15.05 days; 95% CI 7.29-22.80; I^2=90%; very low certainty of evidence) [5,7,9], length of intensive care unit stay (MD +7.82 days; 95% CI 1.59-14.06; I^2=84%; very low certainty) [5,6,9], and overall length of hospital say (MD +12 days; 95 % CI 8.58-15.41; I^2=61%; very low certainty) [5,6,7,12] were observed in the ECMO group; thus, favoring the Non-ECMO group. Time to negative RT-PCR was inconclusive (MD 0 day; 95% CI -2.39 to 2.39; very low certainty) between treatment groups.

Safety outcomes

Serious adverse events significantly associated in the ECMO group were coagulopathy with any serious bleeding (OR 7.79; 95% CI 5.01-12.14; I^2=0%; low certainty) [5,10,11], gastrointestinal bleeding (OR 2.78; 95% CI 1.27-6.08; low certainty) [5], intracranial hemorrhage (OR 12.29; 95% CI 5.98-25.24; low certainty) [5], pneumothorax (OR 7.95; 95% CI 4.77-13.23; very low certainty) [5], and pulmonary embolism (OR 2.62; 95% CI 1.43-4.82; low certainty) [5]. The most common adverse event associated with ECMO was coagulopathy with any serious bleeding. Incidence of infection (OR 1.31; 95% CI 0.14-1.31; I^2=93%; very low certainty) [6,10,11] and ischemic stroke (OR 1.10; 95% CI 0.45-2.68; I^2=0%; very low certainty) [5,11] were all inconclusive.

Table 2. GRADE Summary of Findings for Critical Outcomes

Critical Outcomes	Basis (Number and Type of Studies, Total Participants)	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
All-cause Mortality[5-14] (Unmatched + Matched Cohorts)	10 cohort studies (n=29,843)	OR 0.64	0.41, 0.99	Benefit	Very Low
All-cause Mortality[7,11,14] (Propensity-matched Cohorts)	3 cohort studies (n=718)	OR 0.23	0.10, 0.52	Benefit	Very Low
SAE: Coagulopathy [5,10,11]	3 cohort studies (n=1,706)	OR 7.79	5.01, 12.14	Harm	Low

SAE: Gastrointestinal Bleeding[5]	1 cohort study (n=1,481)	OR 2.78	1.27,6.08	Harm	Very Low
SAE: Intracranial Hemorrhage[5]	1 cohort study (n=1,481)	OR 12.29	5.98, 25.24	Harm	Low
SAE: Pneumothorax[5]	1 cohort study (n=1,481)	OR 7.95	4.77, 13.23	Harm	Low
SAE: Pulmonary Embolism[5]	1 cohort study (n=1,481)	OR 2.62	1.43, 4.82	Harm	Very Low

Abbreviations: **OR**, odds ratio; **SAE**, serious adverse events

Certainty of evidence

Out of 10 cohort studies, six studies were assessed to have high risk of bias due to issues of comparability of intervention and control groups while four studies were assessed to have low risk of bias. Overall certainty of evidence downgraded to very low due to risk of bias and inconsistency. Significant heterogeneity was observed and could be attributed to several clinical factors such as patients' age upon initiation of ECMO, differences in institutional ECMO protocols, and use of co-interventions. Certainty of evidence evaluated using GRADE method is presented in Appendix 7.

B. Use of ECMO in Children with COVID-19 ARDS

Characteristics of included studies

We found one systematic review and meta-analysis [15] which included 44 studies (18 observational studies, four case series, and 22 case reports) on the use of ECMO in children with COVID-19. In this systematic review, 13 observational studies [16-28] (10 case reports [16-17,20-22,24-28], one case series [23], and two registry-based cohort studies [18,19]) included a total of 39 children from Kuwait [16], Germany [17,26], Europe [18,19], USA [20-23,25], Italy [27], and France [28] aged 7 months to 18 years of (median age 11 years) with COVID-19 ARDS. Majority of the patients were males (24 out of 39 patients, 61.54%). Two studies (one case series [23] and one case report [17]) included nine patients (23% of all patients) with COVID-19 ARDS and multisystem inflammatory syndrome in children (MIS-C). VV-ECMO was used in 22 patients (56.41% of all patients). In 3 patients (7.69% of all patients), the mode of ECMO was not clearly stated but ECMO initiation was indicated for COVID-19 ARDS. VA-ECMO was initiated for patients who underwent cardiac arrest and/or shock. Six studies [16,18,19,25-27] with 25 patients (64.10% of all patients) initiated ECMO within 48 hours of mechanical ventilation initiation. Characteristics of included studies is presented in Appendix 8.

Efficacy outcomes

Overall, the mortality in children who received ECMO for COVID-19 ARDS was 23.08% (9/39 cases) by summation. In two registry-based studies [18,19] with 21 patients, mortality was found to be at 13.40% (2/21; 95% CI 1.9-55.5%; I^2=44.1%) [15]. Duration of ECMO therapy ranged from 3 to 20 days (median ECMO duration 9.75 days) [16-19,21,22,25-28].

Safety outcomes

Serious adverse events observed with the use of ECMO were acute kidney injury [17,18,19] (4/39 cases, 10.26%), cerebral hemorrhage [19] including subarachnoid hemorrhage [20] (2/39 cases, 5.13%), cerebral infarction [18,19] (2/39 cases, 5.13%), circuit thrombi [18,25] (2/39 cases, 5.13%), pneumothorax [18] (2/39 cases, 5.13%), pulmonary hemorrhage [18,26] (2/39 cases, 5.13%), gastrointestinal bleeding [18] (1/39 cases, 2.56%), pulmonary embolism [19] (1/39 cases, 2.56%), right atrial thrombosis [19] (1/39 cases,

2.56%), and seizures [18] (1/39 cases, 2.56%). Seven studies [16,21,22,23,24,27,28] recorded no complications with the use of ECMO.

Certainty of evidence

The overall certainty of evidence was very low as studies were based on case reports, case series, and ECMO-only registry-based cohort studies (lack of comparator group) in the analysis of mortality and serious adverse events critical outcomes. Certainty of evidence evaluated using GRADE method is presented in Appendix 9.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
Extracorporeal Life Support Organization[29-30]	Based on the ELSO guidelines, ECMO should not be initiated for patients with end-stage chronic organ failure without anticipated recovery and who are not candidates for durable device or transplant, in severe acute multiple organ failure with anticipated death despite ECMO support, and in severe acute neurologic injury with poor prognosis for recovery. Potential additional contraindications also include long invasive mechanical duration of more than 10 days, patient or surrogate refusal of blood products, inability to receive systemic anticoagulation, ongoing cardiopulmonary resuscitation, significant underlying comorbidities, advanced age, and immunocompromised condition.	Not Stated
COVID-19 Treatment Guidelines[31] As of 31 May 2022	There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of ECMO in adults with COVID-19 and refractory hypoxemia.	N/A
World Health Organization[32]	Recommended that in settings with adequate ECMO resources and expertise, a consideration of referring patients with refractory hypoxemia for initiation of ECMO should be made.	Not Stated
Australian Guidelines on COVID-19[33]	In mechanically ventilated adults with COVID-19 and refractory hypoxemia (despite optimising ventilation, use of rescue therapies and proning), consider using venovenous extracorporeal membrane oxygenation (VV-ECMO) if available, or referring the patient to an ECMO centre. Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in carefully selected patients with COVID-19 and severe ARDS.	Strength of Recommendation Not Set
COVID-19 Treatment Guidelines[31] As of 31 May 2022	The COVID-19 Treatment Guidelines Panel recommends that the use of ECMO should be considered for children with acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C) who have refractory hypoxemia or shock when hemodynamic parameters cannot be maintained or lung-protective strategies result in inadequate gas exchange. Candidacy for ECMO should be determined on a case-by-case basis by the multidisciplinary team.	Expert Opinion Weak Recommendation Statement (CIII)

ONGOING STUDIES AND RESEARCH GAPS

At present, we found no randomized controlled trials on the use of ECMO among patients with COVID-19 ARDS.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

A retrospective multicenter cohort study [12] done in the US in 2021 reported on the direct hospitalization cost with the use of ECMO compared to optimal ventilatory support. Results showed that direct hospitalization cost for ECMO was estimated at US$138,403 ± 99,173 (₱7,645,104.91 ± 5,478.118.17) while direct hospitalization cost optimal ventilatory strategy was estimated at US$48,419 ± 44,799. (₱2,674,685.71 ± 2,474,607.16). Significantly higher direct cost of hospitalization was observed in the ECMO group (MD US$89,984.00, 95% CI US$84,117.34 – US$95,850.66; ₱4,970,536.19; 95% CI ₱4,646,473.63 – ₱5,0007,046.78; low certainty).

Table 5. Cost of Resources

Outcome	Basis (Number and Type of Studies, Total Participants)	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
Direct Cost of Hospitalization	1 cohort study (n=17,456)	MD US$89,984	84,117.34-95,850.66	Significantly Larger Cost with ECMO	Very Low

Cost-effectiveness

An economic evaluation of intensive care unit resources among adult patients with severe COVID-19 was performed in Germany between April 2020 to April 2021 by Schallner et al. [34]. In this economic evaluation study, incremental cost-effectiveness ratio (ICER) for ECMO therapy was determined in 49 patients among which 22 patients were placed on ECMO while 27 patients received standard intensive unit care. Mean direct intensive care unit costs amounted to US$74,584 ± 54,100 (₱4,119,870.99 ± 2,988,375.80) per COVID-19 patient. The study detected no quality adjusted life-year gained through ECMO therapy. Relevant additional costs for ECMO therapy amounted to US$385,812 (₱21,311,483.30). The study concluded that there was no beneficial incremental cost-effectiveness with the use of ECMO. However, the study cited potential selection bias as ECMO was used in more severe COVID-19 cases.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

According to the Health Technology Assessment of the Philippine Department of Health [35], there is limited access to ECMO. As of 2021, there are only 13 ECMO machines in the country, most of which are located in highly specialized centers in Metro Manila. Additionally, ECMO treatment requires extensive resources, which include ECMO trained-specialists, and specialists needed to provide continuing critical care, monitoring, and rehabilitation. The use of ECMO likewise requires highly specialized equipment, supplies, training, and maintenance. Delivering this intervention to a high number of patients particularly during a pandemic can be challenging for the healthcare system. We found no studies regarding patient's values, preference and acceptability in relation to the use of ECMO.

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Appendix 1: Preliminary Evidence to Decision

Table 1a. Summary of initial judgements prior to the panel discussion (N=7/10) ECMO – Adult

FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)	Uncertain (1)		Current practice takes into consideration referring patients with COVID-19 ARDS refractory to lung-protective ventilation for ECMO initiation. However, several practical concerns such as institutional ECMO capability, trained personnel availability, and costs are major considerations considered prior to its initiation.
Benefits	Large (1)	Moderate (3)	Small (2)	Trivial (1)	Based on 10 cohort studies [5-14], **the use of ECMO was associated with significant reduction in all-cause mortality** (OR 0.64, 95% CI 0.41-0.99; I^2=94%; very low certainty).
Harm	Large (1)	Moderate (5)	Small	Trivial (1)	**Serious adverse events significantly associated in the ECMO group were coagulopathy with any serious bleeding** (OR 7.79; 95% CI 5.01-12.14; I^2=0%; low certainty) [5,10,11], gastrointestinal bleeding (OR 2.78; 95% CI 1.27-6.08; low certainty) [5], intracranial hemorrhage (OR 12.29; 95% CI 5.98-25.24; low certainty) [5], pneumothorax (OR 7.95; 95% CI 4.77-13.23; very low certainty) [5], and pulmonary embolism (OR 2.62; 95% CI 1.43-4.82; low certainty) [5]. The most common adverse event associated with ECMO was coagulopathy with any serious bleeding. **Incidence of infection (OR 1.31; 95% CI 0.14-1.31; I2=93%; very low certainty) [6,10,11] and ischemic stroke (OR 1.10; 95% CI 0.45-2.68; I^2=0%; very low certainty) [5,11] were all inconclusive.**
Certainty of Evidence	High	Moderate	Low (2)	Very low (5)	Downgraded to **very low due to risk of bias and inconsistency**.
Balance of effects	Favors treatment (1)	Probably favors treatment (4)	Probably favors no treatment (2)	Uncertain (1)	The use of ECMO among adult patients with COVID-19 ARDS was associated with reduction in mortality but was likewise

							associated with prolonged intensive care unit and length of hospital stay. The use of ECMO among adult patients COVID-19 ARDS was also associated with serious adverse events were coagulopathy with any serious bleeding, gastrointestinal bleeding, intracranial hemorrhage, pneumothorax, and pulmonary embolism.
Values	Important uncertainty or variability (3)		Possibly important uncertainty or variability (2)		Possibly NO important uncertainty or variability (2)	No important uncertainty or variability	
Resources Required	Uncertain		Large cost (7)		Moderate cost	Negligible cost	Moderate savings / Large savings
Certainty of evidence of required resources	No included studies		Very low (2)		Low (4)	Moderate (1)	High
Cost effectiveness	No included studies	Varies (1)	Probably favors the comparison (2)	Favors the comparison (1)	Probably favors the intervention (1)	Favors the intervention	Does not favor either the intervention or the comparison (2)
Equity	Uncertain	Varies	Reduced (1)	Probably reduced (2)	Probably no impact (2)	Probably increased (2)	Increased
Acceptability	Varies (2)		Probably no (2)		Yes	Probably yes (3)	
Feasibility	Varies (3)		No (1)		Yes	Probably yes (3)	

A retrospective multicenter cohort study[12] done in the US in 2021 reported on the direct hospitalization cost with the use of ECMO compared to optimal ventilatory support.
Results showed that **direct hospitalization cost for ECMO was estimated at $138,403 ± 99,173** (₱7,645,104.91 ± 5,478.118.17) while **direct hospitalization cost optimal ventilatory strategy was estimated at $48,419 ± 44,799** (₱2,674,685.71 ± 2,474,607.16).
Significantly higher direct cost of hospitalization was observed in the ECMO group (MD US$ 89,984.00, 95% CI US$ 84,117.34 – US$ 95,850.66 or ₱4,970,536.19; 95% CI ₱4,646,473.63 – ₱5,007,046.78; low certainty).

The study concluded that there was no beneficial incremental cost-effectiveness with the use of ECMO. However, the study cited potential selection bias as ECMO was used in more severe COVID-19 cases.

For the use: 4 (weak)
Against the use: 3 (weak)
No additional considerations or comments

Table 1b. Summary of initial judgements prior to the panel discussion (N=3/10) ECMO – Children

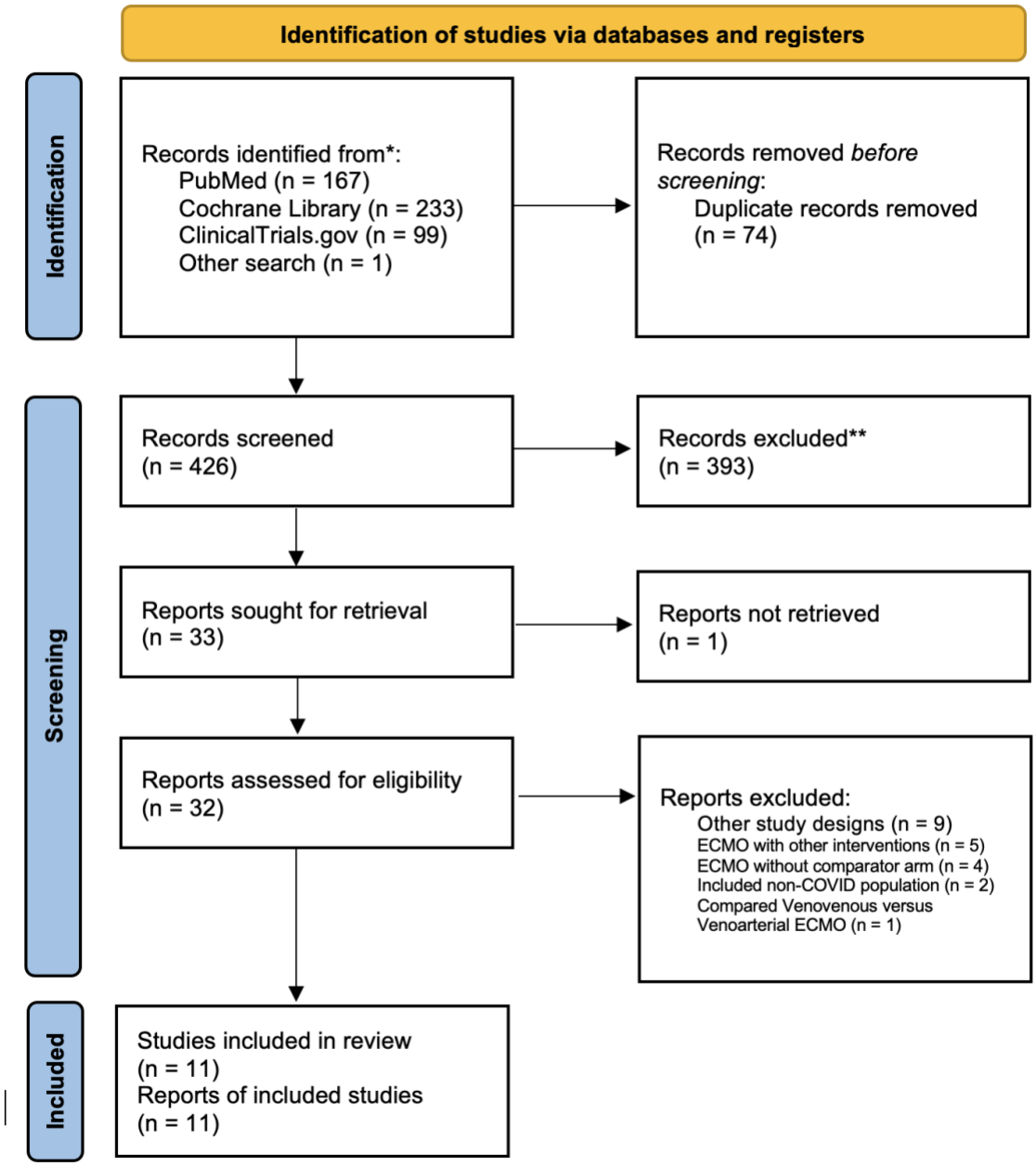
FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (3)			Current practice takes into consideration referring patients with COVID-19 ARDS refractory to lung-protective ventilation for ECMO initiation. However, several practical concerns such as institutional ECMO capability, trained personnel availability, and costs are major considerations considered prior to its initiation.
Benefits	Large	Moderate (1)	Small	Trivial (2)	**Overall, the mortality in children who received ECMO for COVID-19 ARDS was 23.08% (9/39 cases) by summation.**
Harm	Large (2)	Moderate (1)	Small	Trivial	**Serious adverse events observed with the use of ECMO were acute kidney injury [17,18,19] (4/39 cases, 10.26%), cerebral hemorrhage [19] including subarachnoid hemorrhage [20] (2/39 cases, 5.13%), cerebral infarction [18,19] (2/39 cases, 5.13%), circuit thrombi [18,25] (2/39 cases, 5.13%), pneumothorax [18] (2/39 cases, 5.13%), pulmonary hemorrhage [18,26] (2/39 cases, 5.13%), gastrointestinal bleeding [18] (1/39 cases, 2.56%), pulmonary embolism [19] (1/39 cases, 2.56%), right atrial thrombosis [19] (1/39 cases, 2.56%), and seizures [18] (1/39 cases, 2.56%). Seven studies [16,21,22,23,24,27,28] recorded no complications with the use of ECMO.**
Certainty of Evidence	High	Moderate	Low (1)	Very low (2)	The overall certainty of evidence was very low as studies were based on case reports, case series, and ECMO-only registry-based cohort studies (lack of comparator group) in the analysis of mortality and serious adverse events critical outcomes.
Balance of effects	Favors treatment	Probably favors treatment (2)	Favors no treatment (1)	Does not favor treatment	**Overall, the mortality in children who received ECMO for COVID-19 ARDS was 23.08%. Duration of ECMO therapy ranged from 3 to 20 days (median ECMO duration 9.75 days)**. Univariate one-group

								(ECMO-only cases) meta-regression analysis by Watanabe and colleagues showed that VV-ECMO mainly initiated for COVID-19 ARDS could likely be associated with lower mortality (meta-regression coefficient -1.524; 95% CI -6.62 to 3.57; Very low certainty). The association, however, was not statistically significant.
Values	Important uncertainty or variability (1)		Possibly important uncertainty or variability (1)		Possibly NO important uncertainty or variability (1)	No important uncertainty or variability		
Resources Required	Uncertain (2)		Large cost		Moderate cost	Negligible cost	Moderate savings	Large savings	No research evidence for the pediatric population
Certainty of evidence of required resources	No included studies (3)		Very low		Low	Moderate	High	
Cost effectiveness	No included studies (3)	Varies	Probably favors the comparison	Favors the comparison	Probably favors the intervention	Favors the intervention	Does not favor either the intervention or the comparison	
Equity	Uncertain	Varies (1)	Reduced	Probably reduced (1)	Probably no impact	Probably increased (1)	Increased	
Acceptability	Uncertain (1)	Varies (1)	No	Probably no	Yes (1)	Probably yes		**For the use: 2 (weak)** **Against the use: 1 (weak)** **No additional considerations or comments**
Feasibility	Uncertain	Varies (1)	No	Probably no (1)	Yes (1)	Probably yes		

Appendix 2: Search Strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(("COVID"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "sars coronavirus 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel cov"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "ncov 19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "novel coronavirus disease"[Title/Abstract] OR (("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract]) OR "coronavirus disease 2019"[Title/Abstract] OR "corona virus disease 2019"[Title/Abstract] OR "novel coronavirus pneumonia"[Title/Abstract] OR "novel corona virus pneumonia"[Title/Abstract]) AND ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR "ECMO"[All Fields]) OR "extracorporeal membrane oxygenation"[Title/Abstract] OR "ECMO"[Title/Abstract]) AND 2021/11/09:2022/12/31[Date - Publication] AND (("cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields] OR (("prospective"[All Fields] OR "prospectively"[All Fields]) AND ("cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields])) OR (("retrospective studies"[MeSH Terms] OR ("retrospective"[All Fields] AND "studies"[All Fields]) OR "retrospective studies"[All Fields] OR "retrospective"[All Fields] OR "retrospectively"[All Fields] OR "retrospectives"[All Fields]) AND ("cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields]))) AND 2021/11/09:2022/12/31[Date - Publication])) AND (2021/11/9:2022/12/31[pdat])	08-Jan-2023 03:26 AM	167	8
CENTRAL	"COVID-19" AND "ARDS" AND "extracorporeal membrane oxygenation"	08-Jan-2023 05:30 AM	233	2
ClinicalTrials.gov	"COVID-19 Acute Respiratory Distress Syndrome AND "extracorporeal membrane oxygenation"	08-Jan-2023 12:15 PM	99	0
Bibliographic Search	N/A	08-Jan-2023 07:45 PM	1	1

Appendix 3: PRISMA Flow Diagram



Appendix 4: Risk of Bias Assessment for Cohort Studies (Adult Patients)

MODIFIED NEWCASTLE OTTAWA SCALE FOR COHORT STUDIES							
Study ID	SELECTION			COMPARABILITY	OUTCOME		Total Score (out of 7)
	Representativeness of exposed cohort (Maximum: ★)	Selection of non-exposed cohort (Maximum: ★)	Ascertainment of exposure (Maximum: ★)	Comparability of cohorts on the basis of the design or analysis (Maximum: ★★)	Assessment of outcome (Maximum: ★)	Adequacy of follow up of cohorts (Maximum: ★)	
Alhumaid 2021	★	★	★	-	★	★	★★★★★ (5)
Cheng 2021	★	★	★	-	★	★	★★★★★ (5)
Fang 2021	★	★	★	★★	★	★	★★★★★★★ (7)
Hajage 2022	★	★	★	-	★	★	★★★★★ (5)
Ippolito 2022	★	★	★	-	★	★	★★★★★ (5)
Li 2021	★	★	★	-	★	★	★★★★★ (5)
Mustafa 2021	★	★	★	★★	★	★	★★★★★★★ (7)
Nguyen 2021	★	★	★	-	★	★	★★★★★★★ (5)
Urner 2022	★	★	★	★	★	★	★★★★★★ (6)
Whebell 2022	★	★	★	★★	★	★	★★★★★★★ (7)

Appendix 5: Risk of Bias Assessment for Systematic Review

	PICO	Study protocol	Selection of study designs	Comprehensive search strategy	Study selection in duplicate	List of excluded studies justified	Description of included studies in adequate detail	Satisfactory technique for assessing risk of bias	Source of funding for the studies included	Appropriate methods for statistical combination of results	Potential impact of risk of bias in individual studies on metaanalysis	Account for risk of bias in individual studies when interpreting results	Satisfactory explanation and discussion of any heterogeneity	Publication bias	Conflict of interest	Overall confidence
Watanabe 2022	PY[a]	Y	Y	Y	Y	No[b]	Y	Y	No[c]	Y	Y	Y	Y	Y	Y	Moderate

Explanations:

a. Population (pediatric patients aged 18 years and below), intervention (use of extracorporeal membrane oxygenation), and outcomes (mortality) were included in the review. However, the systematic review only included the intervention without comparator.
b. List of excluded studies and justification for exclusion not found.
c. Source of funding for studies included not mentioned

Appendix 6: Characteristics of Included Studies (Adult Patients)

STUDY ID Country Study Designs	AGE		Indications for ECMO	Contraindications for ECMO
	ECMO GROUP	NON-ECMO GROUP Optimized Mechanical Ventilation		
Alhumaid 2021 [5] (Saudi Arabia) Prospective, multicenter observational study	43.17 ± 9.35 (17–65) **ECMO group significantly younger*	56.57 ± 15.18 (15-108)	Guidelines of the Extracorporeal Life Support Organization (ELSO) on COVID-19 were used to help prepare and plan provision of ECMO for patients included in this study during the ongoing pandemic. The extracorporeal membrane oxygenation (ECMO) group included patients who were admitted to the intensive care unit and on invasive mechanical ventilation, and received ECMO as they met the indications for ECMO initiation. ELSO Indications for ECMO initiation were: 1. PaO2:FiO2 ratio< 60 mmHg for > 6 h and/or 2. PaO2:FiO2 ratio < 50 mmHg for > 3 h and/or 3. pH < 7.20 + PaCO2 > 80 mmHg for > 6 ARDS was defined according to the Berlin definition.	Not stated
Cheng 2021 [6] (China) Retrospective multicenter cohort study	58 (IQR 47–66) **ECMO group significantly younger*	66 (IQR 60-76)	According to the protocol, indications for ECMO were: 1. Under optimal ventilation conditions (FiO2 ≥ 0.8, tidal volume at 6 ml/kg ideal weight, PEEP ≥10 cm H2O) 2. If there was no contraindication, occurrence of one or more of the following: a. PaO2:FiO2 ratio <50 mmHg for more than 3 h b. PaO2:FiO2 ratio <80 mmHg for more than 6 h c. FiO2 of 1.0, PaO2:FiO2 ratio <100 mmHg d. pH <7.25 and PaCO2 >60 mmHg for more than 6 h with respiratory rate >35/min e. pH <7.2 and plateau pressure>30 cmH2O even respiratory rate >35/min *f. Severe air leakage syndrome*	Contraindications to ECMO use were: 1. Complicated with irreversible disease 2. Absolute contraindication of anticoagulation 3. Mechanical ventilation lasted for more than 7 days at higher ventilator settings (FiO2 > 0.9, plateau pressure > 30 cmH2O) 4. Vascular anatomical malformations or lesions in the puncture site 5. Advanced age 6. Immunosuppression (absolute neutrophil count <400/mm3)
Fang 2021 [7] (China) Retrospective multicenter matched cohort study	Age ≥60 years (36/70, 51.4%) **Age ≥60 equal in both treatment groups p=0.203*	Age ≥60 years (43/70, 61.4%)	ECMO was considered when protective ventilation and prone-position ventilation were ineffective and one or more of the following criteria were met, despite the application of an optimal ventilatory strategy (FiO2 >0.8 tidal volume of 6 mL kg of predicted body weight, PEEP >10 cm H2O): 1. PaO2:FiO2 ratio <50 mmHg >3 h 2. PaO2:FiO2 ratio <80 mmHg >6 h 3. PaO2:FiO2 ratio <100 mmHg at a FiO2=1.0 4. Arterial pH <7.25 and PaCO2 >60 mmHg >6 h with a respiratory rate >35 breaths/min 5. Arterial pH <7.20 with a respiratory rate >35 breaths/min and plateau pressure >30 cmH2O 6. Cardiogenic shock or cardiac arrest **Veno-venous (VV) ECMO was preferred for patients with normal cardiac function. Veno-arterial (VA) ECMO was applied when cardiogenic shock was diagnosed.*	Relative contradictions included: 1. A combination of irreversible diseases 2. Contradictions to anticoagulation 3. Mechanical ventilation >7 days under high ventilatory settings (FiO2 >0.9 and plateau pressure >30 cmH2O); 4. Immunocompromised status 5. Lack of vascular access for ECMO because of vascular deformity.

STUDY ID Country Study Designs	AGE		Indications for ECMO	Contraindications for ECMO
	ECMO GROUP	NON-ECMO GROUP Optimized Mechanical Ventilation		
Hajage 2021 [8] (France) Emulated Targeted Trial Analysis	52.29 ± 8.9751 53 (IQR 46-58) **Significantly younger in ECMO group* *(MD -7.61 [-9.03, -6.19])*	59.9 ± 9.6417 60 (IQR 53-66)	First, our inclusion criteria for the emulated target trial were on the basis of PaO2/FIO2,80 and/or PaCO2>60mm Hg at one point (regardless of the timing of adjunct therapies during that day), which contrasts with the EOLIA trial and expert recommendations which advocate considering the duration of time (i.e,.6 h) below a PaO2/FIO2 or above a PaCO2 threshold	Not stated
Ippolito 2021 [9] (Germany) Retrospective single-center cohort study	54 ± 12.0 **Significantly younger in ECMO group* *MD -10.00 [-13.25, -6.75]*	64 ± 12.0	According to ELSO Criteria?	?
Li 2021 [10] (China) Retrospective single-center cohort study	64.5 (IQR 56-72) **No significant difference*	59.2 (IQR 65.2-72.2)	ECMO initial criteria: 1. Reversible respiratory failure with hypoxemia a. PaO2:FiO2 less than 50 mmHg for more than 3 h b. PaO2:FiO2 less than 80 mmHg for more than 6 h 2. Arterial blood pH less than 7.25 with a PaCO2 of at least 60 mmHg for more than 6 h with respiratory rate more than 35 breaths per minute 3. Plateau pressure more than 30-35 cmH2O despite optimization of mechanical ventilation.	Contraindications to ECMO: 1. Mechanical ventilation at high settings (FiO2 > 0.9, plateau pressure greater than 30 cmH2O for ≥7 days 2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm3) 3. Recent or expanding central nervous system hemorrhage 4. Non-recoverable comorbidity such as major central nervous system damage or terminal malignancy
Mustafa 2021 [11] (USA) Retrospective multicenter matched cohort study	49.0 ± 1.1 Range: 22-67 **No significant difference*	52.1 ± 1.0 Range: 22-64	The following criteria were used to determine ECMO candidacy: *1. Patients 70 years old and below* 2. Suffering from severe hypoxia or hypercarbia despite maximum ventilatory support similar to what was described by the EOLIA trial group: a. Arterial PaO2:FiO2 of 50mm Hg for >3 h b. Arterial PaO2:FiO2 of 80 mm Hg for >6 h c. Arterial blood pH of 7.25 with PaCO2 60 mm Hg for >6 h d. Maximized ventilator settings constituted of a minimal FiO2 of 0.8, PEEP 10 cm H2O and tidal volumes of 6 mL/kg predicted body weight, while keeping a plateau pressure 32 cmH2O	Absolute contraindications to ECMO: 1. Patients with cardiac arrest without return of spontaneous circulation, lactate 14 mmol/L or pH 6.9 2. In multisystem organ failure involving three or more organ systems 3. Projected life expectancy 5 years before SARS-CoV-2 infection 4. Known devastating neurological injury, recent hemorrhagic stroke or any known major bleeding diathesis 5. Known DNR/DNI status 6. Those who refuse to receive blood transfusions, 7. Those with permanent immobility, known active malignancy 8. Severe, symptomatic chronic organ failure, such as cirrhosis, end-stage renal disease on dialysis, end-stage cardiomyopathy, or those with severe chronic lung disease requiring home oxygen therapy, among others

STUDY ID Country Study Designs	AGE		Indications for ECMO	Contraindications for ECMO
	ECMO GROUP	NON-ECMO GROUP Optimized Mechanical Ventilation		
Nguyen 2021 [12] (USA) Retrospective multicenter cohort study	Age group 18-30: 123 (11.1%) *31-50: 550 (49.4%)* 51-64: 440 (39.5%) **ECMO group significantly younger*	Age group 18-30: 832 (5.1%) 31-50: 5,113 (31.3%) *51-64: 10,398 (63.6%)* **Non-ECMO group significantly older*	Not stated	Not stated
Urner 2021 [13] (Canada) Retrospective multi-country study			ECMO treatment in patients with a PaO2:FiO2 ratio <80 mm Hg and a treatment strategy where all patients received conventional mechanical ventilation without ECMO.	Not stated
Whebell 2022 [14] (United Kingdom) Retrospective multicenter matched cohort study	46 (IQR 40-53) **No significant difference*	48 (IQR 39-55)	Following National Health Service commissioning in 2011, the UK patients with severe respiratory failure (SRF) may be referred to a designated ECMO centre, where specialists perform remote assessment, deliver advice, and consider patients against national eligibility criteria for retrieval on mobile ECMO. Criteria are outlined by NHS England, establishing consistent indications for respiratory ECMO provision. The primary indication is potentially reversible SRF (as indicated by severe hypoxaemia, Murray-score > 3, or uncompensated hypercapnia)	Absence of significant frailty and organ failure severity

Appendix 7: GRADE Evidence Profile Table (Adult Patients)

Author(s): Roy Vincent C. Dubouzet, MD, & Christopher G. Manalo, MD, MSc (cand)
Question: Should extracorporeal membrane oxygenation (ECMO) be used in the management of acute respiratory distress syndrome (ARDS) among adult COVID-19 patients?
Setting: Intensive Care Unit

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	Non-ECMO	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (All studies)												
10	observational studies	serious[a]	serious[b]	not serious	not serious	none	1014/2692 (37.7%)	10007/27151 (36.9%)	**OR 0.64** (0.41 to 0.99)	**133 fewer per 1,000** (from 217 fewer to 4 fewer)	⨁◯◯◯ Very low	CRITICAL
All-cause mortality (Propensity-Matched cohorts)												
3	observational studies	not serious	serious[b]	not serious	not serious	none	101/359 (28.1%)	204/359 (56.8%)	**OR 0.23** (0.10 to 0.52)	**438 fewer per 1,000** (from 511 fewer to 273 fewer)	⨁◯◯◯ Very low	CRITICAL
Duration of Mechanical Ventilation (assessed with: days)												
3	observational studies	serious[a]	not serious	not serious	not serious	none	229	1832	-	MD **15.05 days higher** (7.29 higher to 22.8 higher)	⨁◯◯◯ Very low	IMPORTANT
Length of ICU Stay (assessed with: days)												
3	observational studies	serious[a]	not serious	not serious	not serious	none	233	1856	-	MD **7.82 days higher** (1.59 higher to 14.06 higher)	⨁◯◯◯ Very low	IMPORTANT
Length of Hospital Stay (assessed with: days)												
4	observational studies	serious[a]	not serious	not serious	not serious	none	1349	17896	-	MD **12 days higher** (8.58 higher to 15.41 higher)	⨁◯◯◯ Very low	IMPORTANT
Mean Direct Cost of ECMO (assessed with: US$)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	Non-ECMO	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	1113	16343	-	MD **90 US$ higher** (84 higher to 95 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Unclear comparability of cohorts on the basis of study design and/or analysis in the following studies: Alhumaid 2021, Cheng 2021, Hajage 2021, Ippolito 2021, Li 2021, Nguyen 2021
b. Significant heterogeneity

Author(s): Roy Vincent C. Dubouzet, MD, & Christopher G. Manalo, MD, MSc (cand)
Question: Should extracorporeal membrane oxygenation (ECMO) be used in the management of acute respiratory distress syndrome (ARDS) among adult COVID-19 patients?
Setting: Intensive Care Unit

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	Non-ECMO 2	Relative (95% CI)	Absolute (95% CI)		
Complication: Coagulopathy												
3	observational studies	serious[a]	not serious	not serious	not serious	strong association	49/206 (23.8%)	101/1500 (6.7%)	**OR 7.79** (5.01 to 12.14)	**457 more per 1,000** (from 270 more to 750 more)	⨁⨁◯◯ Low	CRITICAL
Complication: Gastrointestinal Bleeding												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8/92 (8.7%)	46/1289 (3.6%)	**OR 2.78** (1.27 to 6.08)	**64 more per 1,000** (from 10 more to 181 more)	⨁◯◯◯ Very Low	CRITICAL
Complication: Intracranial Hemorrhage												
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	14/92 (15.2%)	20/1389 (1.4%)	**OR 12.29** (5.98 to 25.24)	**163 more per 1,000** (from 72 more to 349 more)	⨁⨁◯◯ Low	CRITICAL
Complication: Pneumothorax												
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	27/92 (29.3%)	69/1389 (5.0%)	**OR 7.95** (4.77 to 12.32)	**345 more per 1,000** (from 187 more to 562 more)	⨁⨁◯◯ Low	CRITICAL
Complication: Pulmonary Embolism												
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/92 (15.2%)	89/1389 (6.4%)	**OR 2.62** (1.43 to 4.82)	**104 more per 1,000** (from 28 more to 245 more)	⨁◯◯◯ Very Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Unclear comparability of cohorts on the basis of study design and/or analysis in the following studies: Alhumaid 2021, Cheng 2021, Hajage 2021, Ippolito 2021, Li 2021, Nguyen 2021

Appendix 8: Characteristics of Included Studies (Pediatric Patients)

Study ID Country	Study design	Indication	Age (in years)	VV-ECMO	VA-ECMO	Total Number of Patients	Number of Mortality	Duration of ECMO Therapy (days)
Alfoudi 2021[16] (Kuwait)	Case report	ARDS	8	1	0	1	0	14
Apostolidou 2021[17] (Germany)	Case report	ARDS + MISC	7	NS	NS	1	1	20
Di Nardo 2021[19] (Europe)	Cohort*	ARDS	11 (6-14)**	1	NS	3	1	7 (7-11)***
Di Nardo 2022[18] (Europe)	Cohort*	ARDS	9 (11-17)**	12	NS	18	1	9.5 (4-18.5)***
Flood 2020[20] (USA)	Case report	ARDS	16	0	1	1	1	NS
Hays 2022[21] (USA)	Case report	ARDS	7 months	1	0	1	0	9
Kakuturu 2021[22] (USA)	Case report	ARDS	15	1	0	1	0	10
Lasa 2022[23] (USA)	Case series	ARDS + MISC	NS	3	5	8	3	NS
Lee 2022[24] (Korea)	Case report	ARDS	17	NS	NS	1	0	NS
Lewis 2020[25] (USA)	Case report	ARDS	16	1	0	1	0	6
Menger 2022[26] (Germany)	Case report	ARDS	4	NS	NS	1	1	17
Moscatelli 2021[27] (Italy)	Case report	ARDS	11	1	0	1	1	3
Zalle 2022[28] (France)	Case report	ARDS	18	1	0	1	0	15

ABBREVIATIONS: ARDS, Acute Respiratory Distress Syndrome; **ECMO**, Extracorporeal Membrane Oxygenation; **MISC**, Multisystem Inflammatory Syndrome in Children; **VA-ECMO**, Veno-arterial ECMO; **VV-ECMO**, Venovenous ECMO; **NS**, Not Specified; **LEGENDS**: ***Registry-based cohort studies; **Median age in years; ****Median duration in days

Appendix 9: GRADE Evidence Profile Table (Pediatric Patients)

Author(s): Roy Vincent C. Dubouzet, MD, & Christopher G. Manalo, MD, MSc (cand)
Question: Should extracorporeal membrane oxygenation (ECMO) be used in the management of acute respiratory distress syndrome (ARDS) among pediatric COVID-19 patients?
Setting: Intensive Care Unit

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality									
13	observational studies	serious[a]	not serious	not serious	serious[b]	none	Overall, the mortality of children receiving ECMO for COVID-19 ARDS was 18.37% (9/49 cases) by summation. In two registry-based studies with 21 patients[18,19], mortality was found to be at 13.4% (2/21; 95% CI 1.9 to 55.5%; I2=44.1%)[18,19]. Duration of ECMO therapy ranged from 3-20 days (median 9.75 days)[16-19,21,22,25-28].	⨁◯◯◯ Very Low	CRITICAL
Serious Adverse Events									
13	observational studies	serious[a]	not serious	not serious	not serious	none	Serious adverse events observed with the use of ECMO were acute kidney injury[17,18,19] (4 cases), cerebral hemorrhage[19] including subarachnoid hemorrhage[20] (2 cases), cerebral infarction[18,19] (2 cases), circuit thrombi[18,25] (2 cases), pneumothorax[18] (2 cases), pulmonary hemorrhage[18,26] (2 cases), gastrointestinal bleeding[18] (1 case), pulmonary embolism[19] (1 case), right atrial thrombosis[19] (1 case), and seizures[18] (1 case). Seven studies[16,21,22,23,24,27,28] recorded complications with the use of ECMO.	⨁◯◯◯ Very Low	CRITICAL

Explanations

a. Lack of comparator (non-ECMO) group
b. Imprecision for the association of lower mortality with VV-ECMO mainly for COVID-19 ARDS

Appendix 10: Forest Plots

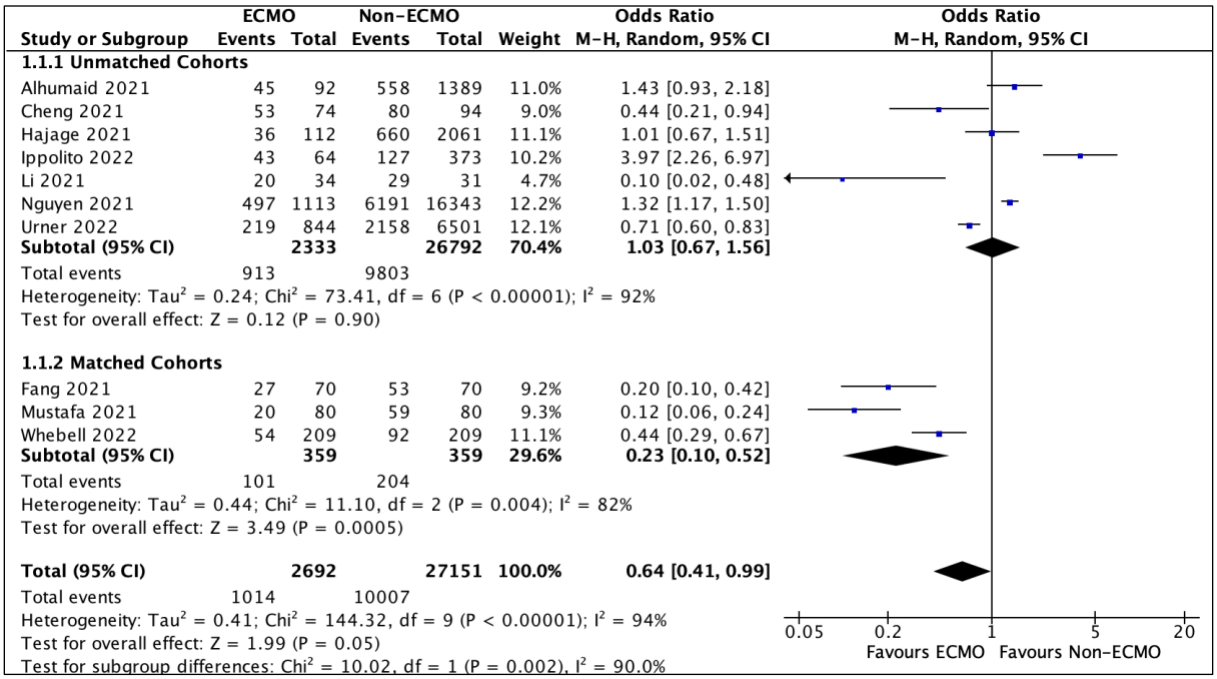


Figure 1. Forest plot for mortality

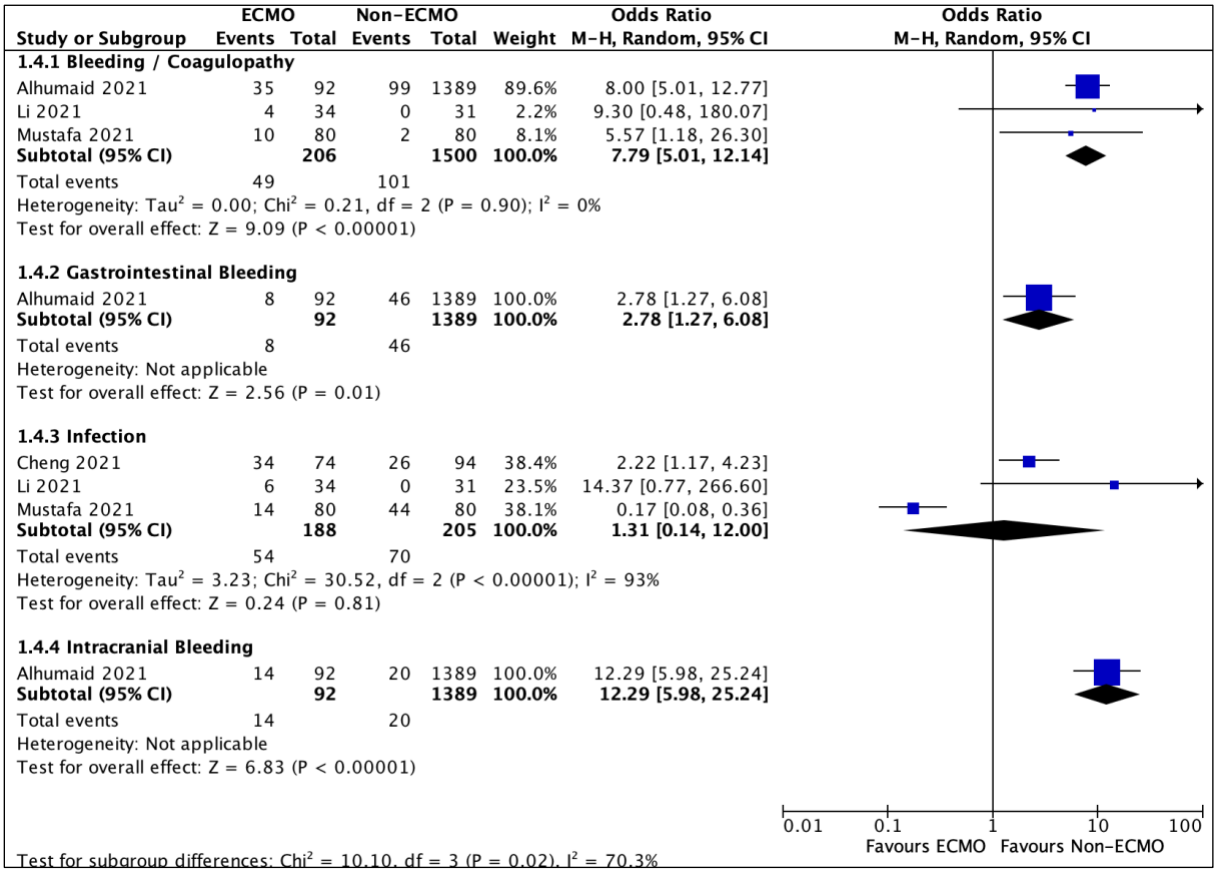


Figure 2. Forest plot for complications

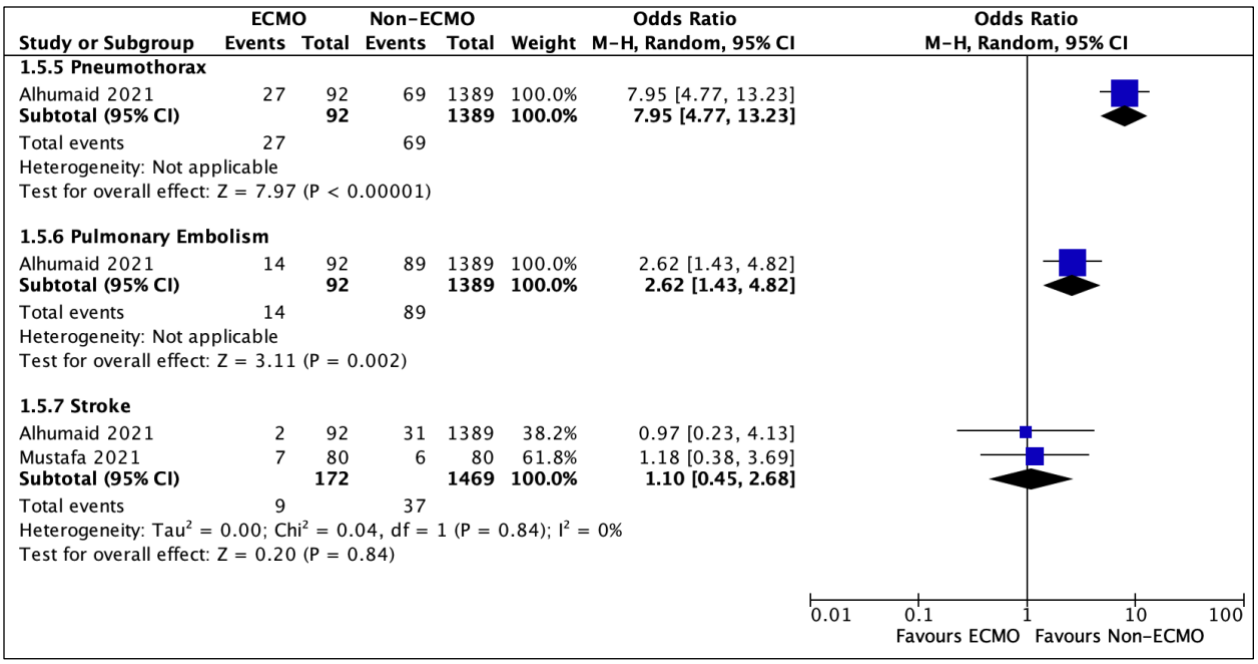


Figure 3. Forest plot for complications

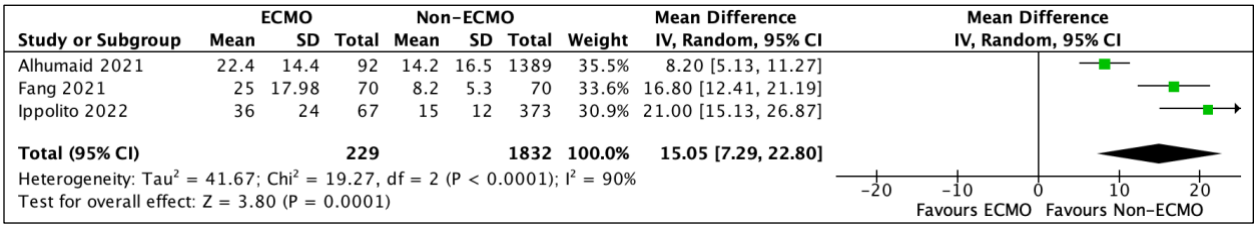


Figure 4. Forest plot for duration of mechanical ventilation

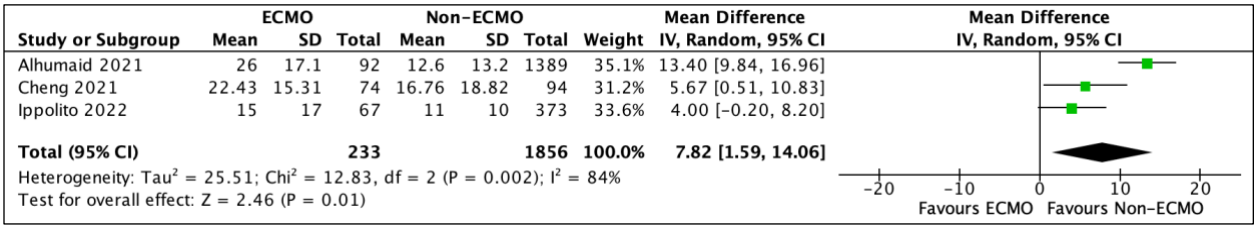


Figure 5. Forest plot for length of intensive care unit stay

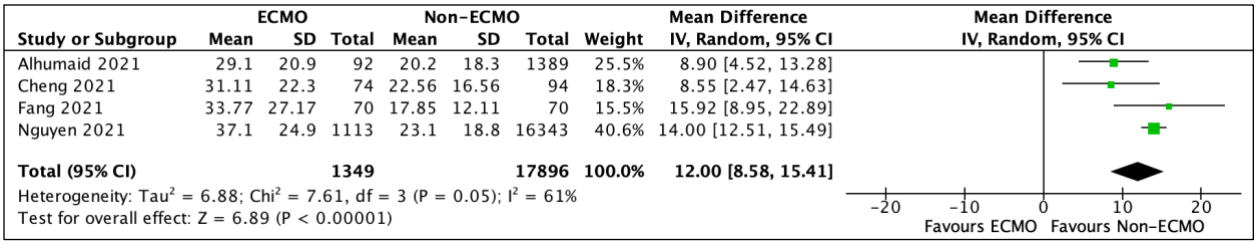


Figure 6. Forest plot for length of hospital stay

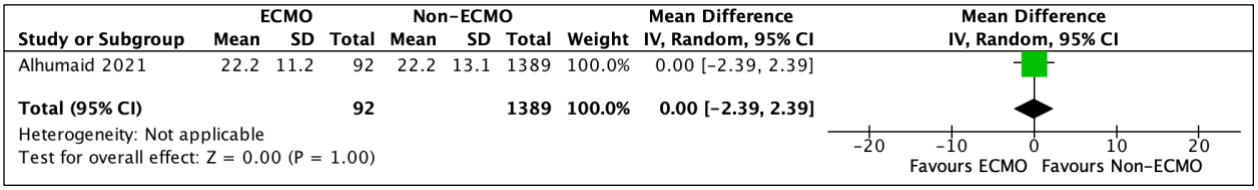


Figure 7. Forest plot for time to negative RT-PCR

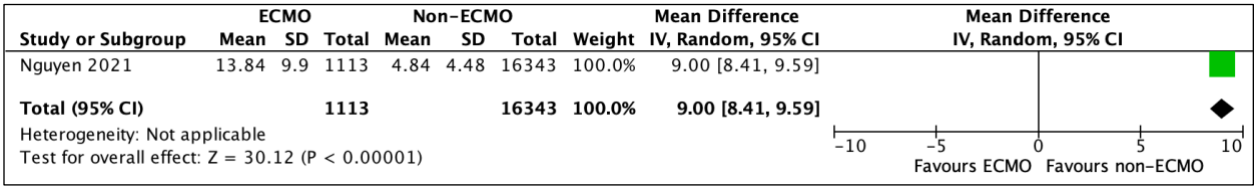


Figure 8. Forest plot for direct cost

NOTE: Mean direct cost of extracorporeal membrane oxygenation x US$ 10,00