Role of extracorporeal membrane oxygenation in COVID-19: A systematic review

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Abstract
Objective: We aimed to examine the literature evidence behind using extracorporeal membrane oxygenation in COVID-19 patients in a systematic review manner.

Methods: We conducted a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A comprehensive literature search was conducted on Global Health Medline, EMBASE, and Cochrane databases using keywords and MeSH terms to identify articles pertaining to extracorporeal membrane oxygenation (ECMO) and Coronavirus disease 2019 (COVID-19). A narrative synthesis was then undertaken to identify the key themes.

Results: A total of 25 articles met the inclusion criteria of this systematic review. Three main themes were identified following the data extraction: (a) evidence against/inconclusive regarding ECMO for COVID-19, (b) evidence supporting ECMO for COVID-19, and finally (c) VV-ECMO and VA-ECMO. After combining the data, there were 3428 patients diagnosed with COVID-19 and 95 ECMO-associated deaths (19.83%).

Conclusion: Our study highlights the paucity of evidence and the need for further data to consolidate the efficacy of ECMO in improving patient outcomes. Although ECMO has been shown to be beneficial in a selected group of patients, the recuperative effects of ECMO remain inconclusive. We must ensure that risk-benefit analysis for each candidate is conducted thoroughly so that patients that have increased probability of survival can benefit from this scarce resource.

KEYWORDS
coronavirus, COVID-19, ECMO, extracorporeal membrane oxygenation

1 INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gathered worldwide attention for its potentially fatal course and complex clinical manifestations. This novel virus primarily affects the cardiorespiratory system, which can lead to acute respiratory distress syndrome (ARDS) and shock.1

Although the studies are ongoing for finding a curative therapy alongside an effective vaccination, the mainstay of management is supportive care at current stage, with a focus on delivering oxygen early in the disease course.2 In March 2020, the World Health
Organisation (WHO) released interim guidelines that advocate the use of extracorporeal membrane oxygenation (ECMO) to support the cardiorespiratory system in patients who fail maximal conventional therapies with ARDS.\(^3\)

ECMO principally functions as a rescue cardiopulmonary bypass, exchanging oxygen with carbon dioxide over an artificial membrane to deoxygenated venous blood which is then returned to the patient via the venous or arterial system. Previous pandemics have proven the role of ECMO to support the recovery from severe respiratory and cardiovascular compromise resulting from ARDS.\(^1,5\) However, the role of ECMO in COVID-19 and its implications are yet to be understood with data being collected and reported from large centers internationally.

This study aims to investigate the current literature and explore the effectiveness of ECMO on patients with COVID-19. Our secondary objective was to identify patterns between types of ECMO (veno-venous [VV] and veno-arterial [VA]), patient characteristics and resultant health outcomes.

2 | METHODS AND MATERIALS

2.1 | 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.

2.2 | Inclusion and exclusion criteria

The main exclusion criteria were narrative reviews, consensus document, 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.

2.3 | Quality assessment

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.

2.4 | Data extraction

Data extracted from the included articles were tabulated, and then, a narrative synthesis was undertaken to identify key themes in the literature.

3 | RESULTS

A total of 102 articles were retrieved from the database search and snowballing. Following the exclusion of duplicates and screening, a total of 25 articles were selected for inclusion in this systematic review\(^6-30\) (Figure 1). The characteristics of these studies are summarized in Table 1.

Three main themes were identified following the data extraction: (a) evidence against/inconclusive regarding ECMO for COVID-19, (b) evidence supporting ECMO for COVID-19, and finally, (c) VV-ECMO and VA-ECMO. In our study, we have identified a total of 3428 patients with COVID-19 and among them 479 patients required ECMO during their stay.

4 | DISCUSSION

ECMO was often adopted as salvage therapy for patients commonly experiencing COVID-19-induced ARDS and/or other COVID-19 complications.\(^6,12,22,27\) The overall mortality rate following the collation of the data from the 25 articles selected in this review was 19.83%. This value can, however, only be used as an estimate as some articles did not report mortality outcomes for their patients put on ECMO, making the mortality rate subject to increase. Despite this, this figure shows a promise that ECMO is not detrimental for critically ill patients with COVID-19.

4.1 | Evidence against/inconclusive regarding ECMO for COVID-19

A small number of studies presented high rates of mortality for patients with COVID-19. Three studies in this review reported 100% mortality for patients with ARDS put on ECMO, whereas Yang et al reported a similarly high mortality rate of 83.33% (15 deaths in total).\(^18,25,26,30\) In addition, Guan et al reported that all five patients that were put on ECMO experienced the composite primary endpoint that consisted of admission to the ICU, use of mechanical ventilation or death.\(^50\)

Other studies reporting poor outcomes for ECMO include Zeng et al.\(^28\) Although three patients did recover following ECMO, four patients (two of which were comatose) remained on ECMO and five patients died. Despite this, however, the study attributed half the deaths to septic shock and multiple organ failure. We are not sure whether the patients in question experienced multiple organ...
failure whilst on ECMO; if this was the case, it would explain the negative outcome due to the absolute contraindication between ECMO and multiple organ failure (as depicted in Extracorporeal Life Support Organisation (ELSO) guidelines). Li et al\textsuperscript{14} depicted rather ambivalent results, reporting a 50% mortality rate. Similarly, Marullo et al\textsuperscript{16} did not indicate any strong conclusions for the use of ECMO, whereby the difference between the number of patients weaned off ECMO (60) and the number of deaths following ECMO (57) was marginal. Both studies, however, highlighted the increased risk of patients over 60 who possessed comorbidities, characteristics that were consistent with the mortality outcomes.

Loforte et al\textsuperscript{15} also reported that three out of four patients were weaned off ECMO, and although a 75% weaning rate appears successful, one of the three weaned patients eventually died after VV-ECMO removal. The final patient died due to severe gastrointestinal bleeding while on ECMO, highlighting the potentially fatal complications associated with ECMO (with bleeding being the most frequent).\textsuperscript{22} Thus, with two patients out of the four eventually expiring, this study also provides no conclusive indication of the effectiveness of ECMO for COVID-19.

Although these studies have reported either negative or equivocal results, several considerations should be noted. Firstly, many of these articles consist of a small sample, and thus, no reliable conclusions can be made. Secondly, some of the articles did not provide information with regard to the patient’s disease severity at the time of ECMO initiation, so we cannot know whether ECMO was perhaps administered too late to have a significant effect in a severely deteriorating patient.

Main risk factors associated with a high mortality rate include age \(\geq 60\) years, various comorbidities (such as cardiovascular disease and diabetes) and low lymphocyte count <0.8 \((\times 10^9/L)\) and D-dimer levels >1 \(\mu\)g/L on admission.\textsuperscript{33} We find that many of the patient deaths reported in this review possessed some of the above characteristics, allowing us to, therefore, assume that such predispositions were potential determinants that had a strong influence on the prognosis of patients, despite the initiation of ECMO.

4.2 | Evidence supporting ECMO for COVID-19

In our study, six case reports and two case series reported positive endpoints (weaned off ECMO/discharged from hospital) for patients on ECMO.\textsuperscript{7,9,11,17,19,23,29} These outcomes supporting ECMO for COVID-19 are likely to have occurred for the following reasons.

First, the literature posited that early timing of ECMO support may have resulted in successful outcomes. Zhan et al and Taniguchi et al indicated that early ECMO provision could have enabled the
| Author          | Country | Study type      | Cohort size (no of patients on ECMO) | Admitted to ICU | ARDS | Time and type of ECMO (VV or VA) | Overall mortality (%) | ECMO prognosis (%) |
|----------------|---------|----------------|-------------------------------------|----------------|------|----------------------------------|----------------------|------------------|
| Barrasa et al  | Spain   | Retrospective  | 48 (1)                             | 48             | 48   | N/A                              | 6 (15)               | N/A              |
| Bemtgen et al  | Germany | Case report    | 1 (1)                              | 1              | 1    | VA-ECMO and then switched to VV ECMO (on day 19 since admission) | N/A                  | Patient stabilized following vasoplegic shock following VA-ECMO |
| Chen et al     | China   | Retrospective  | 99 (3)                             | 23             | 17   | N/A                              | 11 (11)              | 1 death in patient with long history of smoking (33.3) |
| Firstenberg et al | USA | Case report    | 1 (1)                              | 1              | 1    | VV-ECMO (introduced on 7th day) 11d on ECMO in total | N/A                  | Patient taken off ECMO on day 17 and discharged day 28 |
| Guan et al     | China   | Cross-sectional| 1099 (5)                           | 55             | 37   | N/A                              | 14 (1.4)             | 5 (100) experienced composite primary endpoints (admission to intensive care unit, use of mechanical ventilation/deaths) |
| Hartman et al  | USA     | Case report    | 1 (1)                              | N/A            | N/A  | VV-ECMO Started ECMO on hospital day 4 7d on ECMO in total | N/A                  | Patient taken off ECMO on day 7 |
| Huang et al    | China   | Cross-sectional| 41 (2)                             | 13             | 12   | N/A                              | 6 (14.6)             | N/A              |
| Jacobs et al   | USA     | Cross-sectional| 32 (32)                            | N/A            | N/A  | VV-ECMO used in 78.1% of cases   | 10 (31.3)            | 10 deaths (31.3) 5 weaned off (15.6) 17 still on ECMO (53.1) Only patients on VV ECMO survived (5 out of 12 (41.7)) |
| Li et al       | China   | Case series    | 16 (8)                             | N/A            | N/A  | 7 on VV-ECMO 1 on VA-ECMO (during cardiopulmonary resuscitation) | N/A                  | 4 deaths (50) 3 weaned off (37.5) 1 still on ECMO (12.5) |
| Loforte et al  | Italy   | Observational  | 59 (4)                             | 59             | 59   | VV-ECMO used in all patients     | 1 (25)               | 1 death (25) 3 weaned off (75) |
| Marullo et al  | Europe  | Retrospective  | 333 (333)                          | N/A            | N/A  | VV-ECMO used in 93.7% of cases   | 57 (17.1)            | 57 deaths (17.1) 60 weaned off (18.1) |
| Nakamura et al | Japan   | Case report    | 1 (1)                              | 1              | 1    | VV-ECMO introduced on hospital day 2 (illness day 12) 11d on ECMO in total | N/A                  | Patient discharged |
| Ruan et al     | China   | Retrospective  | 150 (7)                            | 41             | 62   | N/A                              | 68 (48.3)            | 7 deaths (100) |
| Shen et al     | China   | Case series    | 5 (1)                              | 5              | 5    | N/A                              | N/A                  | Patient weaned off ECMO |
| Sultan et al   | USA     | Case series    | 10 (10)                            | N/A            | 10   | VV ECMO Median time from first symptom to ECMO: 11d 7 and 10d in total on ECMO | 1 (10)               | 1 death (10) 2 weaned off (20) 1 weaning off (10) |
| Takeda         | Japan   | LTE           | 26 (26)                            | N/A            | N/A  | N/A                              | N/A                  | 16 weaned off (61.5) 10 still on ECMO (38.5) |
| Tang et al     | China   | Retrospective case-control | 179 (10) | 73 | 73 | N/A                              | 21 (28.3)            | N/A |
| Taniguchi et al| Japan   | Case report    | 1 (1)                              | 1              | 1    | VV-ECMO (introduced on 6th day, day 2 after intubation) 6d on ECMO in total | N/A                  | Patient weaned off ECMO on day 12 |
recovery of their patients, whereby their organ oxygen supply was protected and lung injury resulting from mechanical damage (ventilators) was avoided.\textsuperscript{23,29}

Second, Taniguchi et al\textsuperscript{23} highlighted how the use of ECMO to stabilize oxygenation and rest the lungs can also play an important role in improving outcomes. Recognition and treatment of the cause of deteriorating oxygenation are imperative. In the context of this case, the patient may have experienced worsening oxygenation due to aggravation of ARDS by COVID-19 pneumonia. In the cases where inflammatory results were stronger than pulmonary congestion, ECMO was initiated to aid the patient’s recovery.

Third, in cases where the association between COVID-19, cytokine storm and mortality has been established,\textsuperscript{34} the role of ECMO in reducing inflammatory substances has also been attributed to patient survival.\textsuperscript{23} ECMO as a therapeutic adjunct has shown promising results in reducing inflammation when utilized in conjunction with primary treatment.\textsuperscript{9,11,20}

### 4.3 VV-ECMO and VA-ECMO

Two types of ECMO are often used in ARDS: VV and VA.

Within this review, VV-ECMO is the most common type utilized amongst patients, with only two patients receiving VA-ECMO as treatment.

Many of the studies specifying the use of VV-ECMO resulted in positive outcomes.\textsuperscript{7,9,11,15,17,19,21,23,29} For example, Jacobs et al\textsuperscript{13} showed that out of 15 patients placed on ECMO, only 5 were successfully weaned off, all previously placed on the VV variation. The remaining patients were placed either on VA-ECMO or a triple cannulation combination. This is equivalent to a 41.7% survival rate on VV-ECMO compared to a 100% mortality rate on all other combinations.

In contrast, Bemtgen et al\textsuperscript{7} report the successful use of VA-ECMO in a case of mixed cardiogenic and vasoplegic shock. However, it was used in conjunction with a peripheral ventricular assist device which may have aided. Furthermore, the cardiogenic shock in this patient was not a result of the cytokine storm described in ECMO patients, but of an underlying acute or chronic heart failure. The stabilization of the vasoplegic shock, however, may have been attributed to the use of VA-ECMO. Despite this, the complexity of this case means that conclusions regarding the efficacy of ECMO cannot be accurately drawn.

Ruan et al\textsuperscript{18} and Zhou et al\textsuperscript{30} have shown that the accumulation of IL-6 into the circulation is a predictor of fatal outcomes. This supports the use of VA-ECMO as it facilitates the reduction of IL-6 by infusing the blood directly into the arterial circulation and bypassing the lungs. Similarly, Marullo et al\textsuperscript{16} support this notion positinig that VA-ECMO may be more useful than VV-ECMO in protecting the lungs from the cytokine storm (which VV-ECMO can sometimes exacerbate) which can be observed in COVID-19 pneumonia.

The second case of VA-ECMO was reported by Li et al,\textsuperscript{14} whereby ECMO was given during cardiopulmonary resuscitation.
(CPR), unfortunately the patient died 3 hours later. Despite the negative outcome in this particular case, the ELSO guidelines\textsuperscript{31} state that the use of ECMO during CPR is not recommended and has been mentioned as an absolute contraindication (Table 2). This may provide a potential explanation for the outcome experienced by this patient.\textsuperscript{31}

Upon comparing our results to the wider literature, we found that they have similarly endorsed the use of VV-ECMO. According to a systematic review and meta-analysis which included the CESAR\textsuperscript{25} and EOLIA\textsuperscript{56} trials amongst others, the use of VV-ECMO in acute severe respiratory failure was associated with 60-day reduced mortality (RR, 0.73: 95% CI, 0.58-0.92) when compared with conventional mechanical ventilation.\textsuperscript{37} Additionally, ELSO also reported a 40% expected survival to discharge on VA\textsuperscript{38} compared to 58% on VV\textsuperscript{37}; however, this has not been compared to conventional care so the survival advantage of VV is unknown. The CESAR trial has shown survival at 6 months on VV-ECMO to be 63% compared to 47% in the conventional care group ($P = .03$). VA-ECMO was also associated with more complications than VV-ECMO, with the most significant being major hemorrhage (40.8% [26.8%-56.6%]).\textsuperscript{40} Other complications reported are watershed phenomenon due to separated perfusions of the upper and lower body, distension of the left ventricle and resulting increased afterload.\textsuperscript{41}

5 | ALTERNATIVE TREATMENTS

A potential alternative for patients with ARDS outlined in the literature is convalescent plasma. Several studies\textsuperscript{19,42} reported positive outcomes, including decreased need for ventilator use and improvement of clinical symptoms. However, these outcomes could not be attributed solely to the therapeutic use of convalescent plasma. Hence, more evidence including from randomized clinical trials would be necessary to ascertain the safety and effectiveness of its use.

Moreover, ECMO is often considered a last resort therapy in COVID-19 patients. Alternative therapies can, therefore, also encompass palliation. In Italy, Mercadante et al\textsuperscript{13} interviewed the families of patients for hospital-based palliative care. Although most were satisfied by the efforts of the healthcare team, the ability to say good-bye in person was, understandably, perceived irreplaceable. Although beliefs and traditions regarding death vary across cultures around the world, it seems that this final contact is paramount to optimal palliative care.

6 | EVIDENCE-BASED RECOMMENDATIONS

The use of VV-ECMO in COVID-19 ARDS is supported by multiple guidelines.\textsuperscript{3,31,44,45} VV-ECMO provides respiratory support and is most commonly used in severe respiratory failure. As SARS-COV-2 pneumonia is characterized in most cases by acute respiratory failure with some progressing to ARDS, VV-ECMO has been increasingly used. Although the threshold for initiating VV-ECMO varies between sources, general indications include refractory hypoxemia and worsening hypercapnia despite rescue therapies and proning, and single organ failure with none or minor comorbidities.

In contrast, VA-ECMO provides both respiratory and haemodynamic support and is used in cases of cardiogenic shock as a result of cardiac injury, myocarditis, acute myocardial infarction or decompensated cardiac failure. Although there have been no clear guidelines regarding its use in COVID-19 patients, ELSO has provided some indications.\textsuperscript{31} In addition to patient selection criteria for the use of VA-ECMO outside COVID-19, it should be used in patients with refractory cardiogenic shock before the development of multiple organ failure.

Drawing from data published so far, we propose the following algorithm outlined in Figure 2. Patients presumed suitable for ECMO should be identified early, to minimize the risk of complications associated with prolonged ventilator use. We also recommend the absolute contraindications outlined in the guidelines be followed (see Table 2).

In addition to existing guidelines, several prediction tool scores including the PRESERVE ((AUC 0.75 (95% CI, 0.57-0.92; $P = .01$) and RESP scores (AUC 0.81 (95% CI, 0.67-0.95; $P = .035$) have been developed to aid decision-making regarding the use of VV-ECMO based on best predicted outcomes.\textsuperscript{46} The survival after veno-arterial-ECMO (SAVE) score can be used to identify patients that would benefit more from VA-ECMO and balance use with the availability of resources.\textsuperscript{47} However, although these tools have been shown to be good predictors of survival of patients with ARDS placed on VV-ECMO, they do not account for the unique pathophysiology involving the cytokine storm encountered in COVID-19 patients.

In conclusion, as there is currently not enough evidence to support ECMO utilization in COVID-19, we recommend that ECMO should be used with caution and should comply with current

| TABLE 2 Absolute contraindications for ECMO in COVID-19 patients with cardiopulmonary failure (adapted from ELSO)\textsuperscript{31} |
|---|---|
| 1. Advanced age | 2. Clinical frailty scale category ≥3 |
| 3. Severe multiple organ failure (renal failure is not an exclusion criterion) | 4. Severe acute neurological injury |
| 5. Significant underlying comorbidities | 6. Mechanical ventilation >10 |
| 7. Uncontrolled bleeding | 8. Contraindications to anticoagulation |
| 9. Inability to accept blood products | 10. Ongoing CPR |
guidelines. A risk-benefit analysis should be undertaken for patients, and all decisions should be made on a case-by-case basis.

7 | LIMITATIONS

There is paucity of the data in regard of ECMO utilization in COVID-19 due to the either small-sized studies, limited reported outcomes or retrospective nature of the studies which comes with possible selection and reporting bias. Therefore, no reliable overarching conclusions can be made on ECMO utilization for COVID-19. However, this can perhaps be explained by the fact that ARDS (for which VV-ECMO is used) is far more prevalent among COVID-19 patients compared to those with shock (where VA-ECMO is used).
8 | FUTURE RESEARCH

The use of ECMO in COVID-19 patients is a topic that still requires extensive research before significant recommendations can be made. More data are required in terms of prognosis for patients to be put on both VV and VA-ECMO so that we can make reliable conclusions on when and on whom this treatment should be used. Future prospective multi-center studies should be done to validate findings in a larger cohort of patients. These should try to quantify the true isolated effect on COVID-19 outcomes, whilst adjusting for significant covariates such as comorbidities and age, which also have a large influence over patients’ outcomes.

More research should also be conducted on the effectiveness of blood filters such as Cytosorb, which can be used during ECMO treatments to remove cytokines and ease the stress on the cardiovascular and respiratory systems, thereby helping mitigate cytokine-storm-related complications. Although there have been several studies proving its benefits and it has been approved by the FDA, more clinical trials are needed for a conclusive answer regarding its use in COVID-19.48-50

9 | CONCLUSION

Although ECMO has been shown to be beneficial in a selected group of patients, the recuperative effects of ECMO remain inconclusive within the literature. Studies that have reported positive outcomes often describe patients that possess characteristics that have presumptive compatibility with the main indications of ECMO. Therefore, we must ensure that a risk-benefit analysis for each candidate is conducted thoroughly so that patients that have increased probability of survival can benefit from this scarce resource.

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