Mortality with ECMO in critically ill patients with SARS-CoV-2 infection during the COVID-19 pandemic. A systematic review

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ABSTRACT

Introduction and objectives: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an infectious disease that can present as adult respiratory distress syndrome (ARDS). Without an effective drug therapy, extracorporeal membrane oxygenation (ECMO) is essential when invasive mechanical ventilation fails in severe cases. Our study carried out a systematic review of the studies published in 2020 to analyze the mortality of patients with ARDS due to SARS-CoV-2 who required ECMO.

Methods: A systematic review was conducted on Medline combining keywords on SARS-CoV-2 and ECMO. All studies published during 2020 with positive cases of SARS-CoV-2 treated with ECMO were included, whether observational studies or case series. However, due to the heterogeneity in the methodology of the studies, a proper statistical analysis could not be carried out, which ended up limiting our findings.

Results: Our research identified 41 publications during this period including 2007 cases of patients with severe SARS-CoV-2 infection who required invasive support with ECMO. Among these, 985 (49%) improved clinically and were decannulated or discharged from the hospital, while 660 (32.8%) died despite invasive mechanical support. Only 357 patients (17.7%) still needed ventilation support with ECMO at the time of publication of these studies without describing the final clinical outcome.

Conclusions: ECMO therapy could be useful in patients with ARDS due to SARS-CoV-2 according to the recommendations established in the clinical guidelines and based on the availability of financial resources during the pandemic. Conducting a randomized clinical trial comparing the use of ECMO with conventional invasive ventilatory therapy would provide more evidence on this regard and, consequently, more data on the management of severe SARS-CoV-2 infection.


Mortalidad con ECMO en pacientes críticos infectados por SARS-CoV-2 durante la pandemia de COVID-19. Una revisión sistemática

RESUMEN

Introducción y objetivos: El coronavirus del síndrome respiratorio agudo grave de tipo 2 (SARS-CoV-2) genera una enfermedad infecciosa que puede presentarse como síndrome de distrés respiratorio del adulto (SDRA). Sin un tratamiento farmacológico eficaz, el oxigenador extracorpóreo de membrana (ECMO) es fundamental cuando en los casos graves fracasa la ventilación mecánica invasiva. Presentamos una revisión sistemática de los trabajos publicados en el año 2020 para analizar la mortalidad de pacientes con SDRA por SARS-CoV-2 que precisaban ECMO.

Métodos: Se realizó una revisión sistemática en Medline combinando palabras clave sobre SARS-CoV-2 y ECMO. Se incluyeron todos los estudios publicados durante el año 2020 que registraran casos positivos de SARS-CoV-2 tratados con ECMO, ya fueran estudios observacionales o series de casos. Sin embargo, debido a la heterogeneidad en la metodología de los trabajos, no se pudo llevar a cabo un análisis estadístico adecuado, lo cual limita los hallazgos.
INTRODUCTION

In 2020, the World Health Organization (WHO) declared a public health emergency of international concern on a new strain of coronavirus different from the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) with which it shares some similar characteristics. This new strain known as severe acute respiratory syndrome type 2 (SARS-CoV-2) causes an infectious disease called COVID-19 (coronavirus disease-2019) by the WHO. The first case ever reported occurred in Wuhan, China, in December 2019. Since then, the number of contagions and deaths attributed to COVID-19 has been growing with unprecedented numbers. Until January 2021, a total of 91,492,398 and 2,252,164 cases of COVID-19 had been diagnosed worldwide and Spain, respectively. A total of 1,979,507 deaths due to this virus have been confirmed across the world. In Spain 516 cases have required ICU admission, and 53,314 deaths have been reported.

Clinical signs are varied and go from upper respiratory tract infections to severe respiratory distress. It is possible that the intensity of the clinical response is associated with the level of expression of proinflammatory cytokines. As a matter of fact, the cases that end up in an intensive care unit show overexpression of cytokines, mainly IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), macrophage inflammatory protein-1 alpha (MIP-1α), and tumor necrosis factor alpha (TNFα). This mechanism contributes to the development of acute respiratory distress syndrome (ARDS). Patients who develop ARDS and survive have high chances of dying due to pulmonary fibrosis in the future. An autopsy study of patients dead due to ARDS conducted in 2013 found that the prevalence of pulmonary fibrosis with a 1 to 3 weeks clinical course was 24%. However, when the duration of ARDS was > 3 weeks, prevalence went up to 63%. As a matter of fact, ARDS survivors showed reticular patterns in the computed tomography scan in up to 85% of the cases. This reticular pattern is often found on a CT scan in the acute phase of patients with COVID-19.

Although the lung is the organ most commonly affected in severe cases, SARS-CoV-2 infections can damage other organs and progress to multiorgan failure. Several drugs have been used during this pandemic, but none has improved survival to this date. The management of ARDS in severe cases of COVID-19 includes invasive mechanical ventilation, muscle relaxation, and prone positioning. When these measures fail, and for the lack of an effective drug therapy, the Extracorporeal Life Support Organization guidelines suggest the use of extracorporeal membrane oxygenation (ECMO).

The use of ECMO has proven beneficial to treat ARDS due to other viral infections. During the 2009 pandemic caused by the H1N1 influenza virus, mortality went down 21% in Australia and New Zealand in patients treated with ECMO after developing ARDS. These data were similar to those obtained in the United Kingdom during this same pandemic (mortality rate dropped 23% in patients on ECMO vs 52% in patients without it). Also, refractory respiratory distress due to MERS-CoV studied in 2014-2015 in Saudi confirmed a lower in-hospital mortality rate in the group of patients treated with ECMO.

Therefore, the main objective of our study was to conduct a systematic review of mortality in patients with severe SARS-CoV-2 infection who required invasive support with ECMO after developing ARDS refractory to conventional therapy.

METHODS

A systematic review was conducted following the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A combination of the following keywords was used in Medline: «COVID-19», «ECMO», «SARS-CoV-2», «extracorporeal membrane oxygenator» «extracorporeal membrane oxygenation», «mortality», and «ARDS». Inclusion criteria were studies from 2020, whether observational studies or case series, that analyzed the mortality of patients with ARDS and SARS-CoV-2 infection treated with ECMO. Exclusion criteria were publications on ECMO and COVID-19 that would not include additional patients eligible for this research, with the objective of focusing on ECMO related complications, that proved its benefits compared to other therapies, with authors reporting on isolated case reports including children, pregnant and postpartum women with COVID-19 who required ECMO. However, due to the heterogeneous methodology of the studies included a proper statistical analysis could not be conducted. The study was conducted in observance of the Declaration of Helsinki regarding ethical principles on medical research with human beings. This study was approved by the Complejo Hospitalario Universitario ethics committee of the Canary Islands, Spain.

**Abbreviations**

We present a systematic review of publications on patients with severe SAR-CoV-2 infections treated with ECMO during 2020 since the beginning of the COVID-19 pandemic. This study includes one of the largest series of patients requiring ECMO due to severe SARS-CoV-2 infection published on the medical literature to this date.

The main clinical presentation of COVID-19 is a mild infection with dry cough and fever as the most common symptoms; the overall rate of ARDS is 3.4%. However, after studying series of patients who develop pneumonia and require hospitalization, the rate of ARDS can be up to 17% to 21%. The systemic inflammatory response of patients infected with COVID-19 can affect, to a greater or lesser extent, the pulmonary epithelium and endothelium. However, the endothelium seems less affected by SARS-CoV-2, which produces fewer alveolar exudates, thus contributing to the production of dry cough. On the other hand, in patients with severe COVID-19 ARDS does not show the reduction of compliance that a standard ARDS would cause, suggestive that other mechanisms are responsible for severe hypoxemia. This milder endothelial aggression can contribute to a small viral affection of distal organs.

Myocardial damage is present in 7.2% to 20% of the cases and kidney injuries in 2.9% to 15% depending on the sources. Myocardial damage can be associated with higher in-hospital mortality and should tip us off to discard cardiogenic shock due to fulminant myocarditis in case of hemodynamic instability after severe SARS-CoV-2 infection. Myocardial damage is multifactorial and could be the result of the virus direct cardio toxicity on cardiomyocytes. This possibility may be associated with the compatibility that exists between the virus and the angiotensin-II receptor, present in over 7.5% of cardiomyocytes. We should not forget the systemic inflammatory response following the infection that can cause the direct inflammation and suppression of myocardial contractility. Similarly, the fewer visits to the emergency room due to acute coronary syndrome reported and the drop in the activity of the infarction code during the pandemic have both increased the rate of cardiogenic shock of ischemic origin. This has reduced the healthcare activity provided during the pandemic with fewer coronary interventions being performed. This serious complication may have increased the need for ventricular assist devices, particularly ECMO, in the context of a lower availability of this device due to being used by patients with severe SARS-CoV-2 infection.

To fight severe COVID-19 cases due to ARDS refractory to protective invasive mechanical ventilation, muscle relaxation, and prone positioning or cardiogenic shock refractory to inotropic and vasopressor support, VV-ECMO or VA-ECMO are available options according to the guidelines recently published by the Extracorporeal Life Support Organization (ELSO). The problem with this therapy is that it is an expensive and limited resource. Therefore, during this health crisis, it should be used in young populations with high mortality rates and fewer comorbidities. Kidney disease is not an absolute contraindication and it should not be used in patients on invasive mechanical ventilation for more than 7 days because of the worse outcomes reported. For all these reasons, thorough assessments prior to indicating the most appropriate ECMO support is needed in patients with severe SARS-CoV-2 infection. The best time to implant this device is when protective invasive mechanical ventilation and prone positioning fail, and as long as the patient does not develop septic shock or multiorgan failure. After implantation, it is recommended to assess the blood concentrations of IL-6 and lymphocytes because if the numbers of these markers do not improve with this therapy, these patients’ prognosis is often less promising.

The search conducted found higher mortality rates in patients who received ECMO due to ARDS after severe SARS-CoV-2 infection compared to those who developed the disease caused by the H1N1 pandemic.
Table 1. Registry of the studies available, number of patients on extracorporeal membrane oxygenation (ECMO), and number of patients released from the hospital, deceased, and still on ECMO by the time this study was being published

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Patients with COVID-19</th>
<th>Mean age, years (range)</th>
<th>Sex masculine/feminine</th>
<th>Total Patients on ECMO</th>
<th>Patients on VV- or VV/VA- or VAV-ECMO</th>
<th>Patients decannulated or released from the hospital (%)</th>
<th>Dead patients (%)</th>
<th>Patients still on ECMO (%)</th>
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<td>Total</td>
<td></td>
<td>6636</td>
<td>54 (44-71)</td>
<td>1448/457</td>
<td>2007</td>
<td>1545/84</td>
<td>985 (49%)</td>
<td>660 (32.8%)</td>
<td>357 (17.7%)</td>
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(Continues)
influenza virus in the United Kingdom during the pandemic of 2009: 32.8% vs 23%, respectively. These findings are consistent with those from the registry conducted by Barbaro et al., one of the largest registries ever published, of 1035 patients with a 39% in-hospital mortality rate. On the other hand, during the MERS-CoV pandemic of 2015, the mortality of the group that received ECMO therapy was analyzed (64% compared to 100% in the group without this device). However, due to the lack of clinical trials in the pandemic of 2015, the mortality of the group that received ECMO support in these patients may be acceptable for the lack of other therapeutic options. However, every case should be treated with caution. For example, during the pandemic of 2009, much more ECMO systems were used, which may have generated higher mortality results may be different too.

Finally, Melhuish et al. grouped 331 cases from 10 different studies and 4 database registries and estimated a 46% mortality rate. A common limitation of these studies is that none of them includes the registry conducted by Barbaro et al., the largest published to this date. Our review widens and consolidates these findings after including the 3 largest series published to this date of 83, 333, and 1035 patients. Although we found a higher mortality rate compared to the H1N1 pandemic of 2009, ECMO support in these patients may be acceptable for the lack of another therapeutic option. However, every case should be treated individually; patients over 60 and with associated comorbidities like cardiovascular disease and diabetes have a higher mortality risk.

During the first few months of 2020, 2 meta-analyses of patients with SARS-CoV-2-induced ARDS treated with ECMO were conducted. The first one included 4 Chinese studies and proved the poor benefits of this therapy in 17 patients since only 1 managed to survive. The other meta-analysis includes 6 series of 17 patients in total. Fourteen of these patients died and mortality rate was close to 82.3%. The limitation of these studies is the small number of patients included for analysis and both recommended conducting new studies.

There are reviews already currently available on the medical literature. However, one of them only includes 274 patients who required ECMO, meaning that mortality could not be properly analyzed since 45.6% of the patients remained hospitalized by the time the studies included were being published. A different review of 479 patients from 25 studies showed a 19.83% mortality rate. However, the authors claim that it is just an estimate since some of the studies did not report on the mortality rate of the subjects. Finally, Melhuish et al. grouped 331 cases from 10 different studies and 4 database registries and estimated a 46% mortality rate. A common limitation of these studies is that none of them includes the registry conducted by Barbaro et al., the largest published to this date. Our review widens and consolidates these findings after including the 3 largest series published to this date of 83, 333, and 1035 patients. Although we found a higher mortality rate compared to the H1N1 pandemic of 2009, ECMO support in these patients may be acceptable for the lack of another therapeutic option. However, every case should be treated individually; patients over 60 and with associated comorbidities like cardiovascular disease and diabetes have a higher mortality risk.

Due to the complexity of ECMO support, the need for the proper learning curve and clinical experience, the results of this therapy can be biased. From 2003 through 2019, the number of centers that used this device across the world quadrupled, and the number of devices implanted has multiplied by a factor of 6. This is so to such an extent that during an unexpected pandemic when resources need to be immediately restructured, the results obtained by the studies within the first few months of 2020 should be interpreted with caution. For example, during the pandemic of 2009, much more ECMO systems were used, which may have generated higher chances of recovery compared to the current limitation of resources available for the implantation of this device. This means that mortality results may be different too.

Finally, we should mention that despite the fact that patients survive with the invasive support provided by ECMO, the chances of experiencing pulmonary fibrosis in the future are non-negligible with the corresponding higher mortality rate. Further studies are needed to identify patients with greater chances of developing this

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Patients with COVID-19</th>
<th>Mean age, years (range)</th>
<th>Sex masculine/feminine</th>
<th>Total Patients on ECMO</th>
<th>Patients on VV- or VV/VA- or VAV-ECMO (%)</th>
<th>Patients decanulled or released from the hospital (%)</th>
<th>Dead patients (%)</th>
<th>Patients still on ECMO (%)</th>
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<td>Yao K et al.</td>
<td>J Infect Chemother</td>
<td>101</td>
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<td>Zhang J et al.</td>
<td>ERJ Open Res</td>
<td>43</td>
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<td>Zhou F et al.</td>
<td>Lancet</td>
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COVID-19, coronavirus disease-2019; ECMO, extracorporeal membrane oxygenation; NA, not available; VA, venoarterial; VAV, veno-arteriovenous; VV, venovenous; VVV, venovenovenous.

* Study age range.

1 Indication for VA- or VAV-ECMO not available.

4 Incomplete data.
complication; also, antithrombotic therapy may be useful for the management of SARS-CoV-2 infections causing parenchymal pulmonary fibrosis.5

Limitations

The first limitation of our study is that unpublished multicenter registers on scientific journals were excluded.34 Also, patients treated with ECMO from studies focused on analyzing ECMO related complications and isolated case reports were excluded. The characteristics of patients from each study or the methodologies used have not been compared because they were different.

CONCLUSIONS

We believe that invasive support with ECMO may be useful for certain patients based on the recommendations established by the clinical guidelines and the availability of resources despite the dissimilar results obtained. A randomized clinical trial comparing the use of ECMO to conventional invasive mechanical ventilation would bring further evidence on this regard.

FUNDING

This study received no funding whatsoever.

AUTHORS’ CONTRIBUTIONS

N. Báez-Ferrer was involved in the reference search, data analysis, and writing of this manuscript. A. Bompart-Cairós, and D. López-Rial both participated in the reference search. P. Abreu-González, and D. Hernández-Vaquero participated in the review and writing of this manuscript. A. Domínguez-Rodríguez conducted the manuscript final review.

CONFLICTS OF INTEREST

None reported.

WHAT IS KNOWN ABOUT THE TOPIC?

– ARDS can be the clinical presentation of SARS-CoV-2 infection.

– Multiple drug therapies fail during the management of this entity. The use of ECMO is especially important in patients who are refractory to mechanical ventilation, muscle relaxation, and prone positioning.

– Since the beginning of the COVID-19 pandemic and all across 2020 several articles of patients with severe SARS-CoV-2 infection manifested as ARDS have been published. These articles have analyzed the mortality rate associated with ECMO therapy. However, to this date, no randomized clinical trial has assessed the clinical benefit of ECMO in these patients.

WHAT DOES THIS STUDY ADD?

– We presented the results of a systematic review of the studies published in 2020 during the COVID-19 pandemic to analyze the mortality rate of patients with SARS-CoV-2-induced ARDS requiring ECMO.

– A total of 41 publications were identified during 2020, and 2007 cases of patients with severe SARS-CoV-2 infection who required invasive support with ECMO were collected.

– Of all the cases collected, a mortality rate associated with ECMO in patients with severe SARS-CoV-2 was found to be 32.8%; 660 patients died despite therapy with invasive mechanical support.

– ECMO therapy may be useful in patients with SARS-CoV-2-induced ARDS. However, it would be interesting to conduct a randomized clinical trial to compare the use of ECMO to conventional invasive ventilation therapy during this pandemic.

REFERENCES


