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Review Article

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Efetividade da oxigenação por membrana extracorpórea (ECMO) no tratamento de pacientes com Covid-19: revisão sistemática

Effectiveness of extracorporeal membrane oxygenation (Ecmo) in the treatment of patients with Covid-19: systematic review

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Abstract

Introduction: The use of Extracorporeal Membrane Oxygenation (ECMO) has been studied in the treatment of patients with COVID-19, since this therapy has already shown favorable results in the treatment of other pathologies. **Objectives:** Analyze the effectiveness of the use of ECMO in patients with severe acute respiratory failure caused by COVID-19. **Material and Methods:** For the articles selection, it was used the controlled descriptors (DECS): ("Extracorporeal Membrane Oxygenation *" OR ECMO OR "Extracorporeal Life Support *" OR ECLS) and ("COVID *" OR Coronavirus OR "SARS *"). The searches were made in the COCHRANE LIBRARY, PubMed, EMBASE and CINAHL databases. Revisions, editorials, congress abstracts and study protocols were excluded. The variables analyzed were: The benefits and safety of this treatment, as well as whether there was a reduction in the mortality rate, contraindications and risks with this treatment. **Results:** After consulting the databases, 292 articles were identified using the descriptors mentioned above, of which 11 were included in this study after the selection process. The patients who needed ECMO were predominantly elderly that had as risk factors: systemic arterial hypertension (SAH), meningococcal disease (MD) and obesity. The main complications found were hemorrhagic and thromboembolic. The main complications were found in hemorrhagic and thromboembolic phenomenons. **Discussion:** Concerning the laboratory characteristics, it can be mainly observed an increase of the lactate level, lymphopenia and reactive protein C. The found data goes against the other studies about the subject. **Conclusion:** Therefore, as it is a recently studied health condition, it is necessary that further studies are conducted to confirm the efficacy of ECMO in patients with COVID-19.

Keywords: ECMO, extracorporeal membrane oxygenation, COVID-19.

Resumo

Introdução: O uso da Oxigenação por Membrana Extracorpórea (ECMO) vem sendo estudado no tratamento de pacientes com COVID-19, uma vez que essa terapia já demonstrou resultados favoráveis em outras patologias. **Objetivos:** Verificar a efetividade do uso da ECMO nos pacientes com insuficiência respiratória aguda grave causada pelo COVID-19. **Material e Métodos:** Para seleção dos artigos utilizou-se os descritores controlados (DECS):

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("Extracorporeal Membrane Oxygenation*" OR ECMO OR "Extracorporeal Life Support*" OR ECLS) AND ("COVID*" OR Coronavirus OR "SARS*"). As buscas foram realizadas nas bases de dados COCHRANE LIBRARY, PubMed, EMBASE e CINAHL. As variáveis analisadas foram os benefícios e a segurança deste tratamento, bem como se houve a redução da taxa de mortalidade, as contra-indicações e os riscos com esse tratamento. **Resultados:** Após a consulta nas bases de dados 292 artigos foram identificados utilizando os descritores mencionados acima, dos quais 11 foram incluídos nesse estudo após todo o processo de seleção. Os pacientes que necessitaram de ECMO eram predominantemente idosos que possuíam como fatores de risco: hipertensão arterial sistêmica, doença meningocócica e obesidade. As principais complicações encontradas foram fenômenos hemorrágicos e tromboembólicos. **Discussão:** As características laboratoriais, pode-se observar principalmente um aumento do nível de lactato, linfopenia e aumento da proteína C reativa. Os dados encontrados vão de encontro a outros estudos sobre o tema. **Conclusão:** Portanto, por se tratar de uma condição de saúde recentemente estudada, é necessário que novos estudos sejam conduzidos para confirmar a eficácia da ECMO em pacientes com COVID-19.

Palavras-chave: ECMO, oxigenação por membrana extracorpórea, COVID-19

Introduction

In the period of december 2019, the province of Wuhan, located in the central region of China, registered the first case of viral pneumonia associated with severe respiratory failure[1]. The responsible agent, SARS-Cov-2, causes the disease named as COVID-19[1]. Since then, the disease has been spread all over the world, being recognized as a pandemic by the World Health Organization (WHO) in March 2020[1]. Despite a significant proportion of the individuals being asymptomatic or presenting mild symptoms, approximately 15 to 20% of the ill might develop severe forms of the disease, needing intensive therapy and respiratory support in consequence of the severe acute respiratory syndrome (SARS)[2].

Hong X et al. recently identified that, of the 138 patients diagnosed with COVID-19, 26,1% needed intensive care, of which 61,1% evolved to SARS[3]. Currently, the mortality rate in critical cases might reach 61,5%, and no specific treatment was proven until the moment[3,4]. In cases of refractory hypoxemia, in other words, severe cases of SARS, in which occurs a maintenance of the respiratory failure status in spite of inundation and the collapse of the airway spaces, stopping the intake of inhaled gas, the direction of the cases becomes harder, since all of the possibilities with proven scientific evidence are scarce[5,6].

Thus, advanced support therapies with scientific evidence are still not completely established in COVID-19, as the cardiopulmonary support techniques that must have its risks and benefits evaluated[6]. The oxygenation by extracorporeal membrane (ECMO) it's a form of cardiopulmonary support by long period, in which the blood it's drained from its initial location and returned to circulation after going through an oxygenator by membrane and heat transformer[2]. In the context of acute respiratory failure of viral infectious origin, there are some reports previous to COVID-19 about the use of ECMO, mainly referred to the A H1N1 influenza, in the year of 2009[6].

Although there's no randomized controlled trials with the subject of COVID-19, some recommendations of the WHO and Extracorporeal Life Support (ELSO) were published. ELSO is an organization responsible for the protocols of use, register, information and research in ECMO at worldwide level. According to WHO, ECMO can be used in patients with refractory hypoxemia despite the recommended measures, as long as it's carried out in specialized centers of ECMO handling[3,7,8]. Furthermore, ELSO indicates ECMO to patients with high chance of fatal disclosure, primarily to SARS cases that evolve with persistent refractory hypoxemia, with blood oxygen saturation

value (Spo02) minor to 80% over 6 hours or less than 50% for 3 hours. Or in patients with secondary organic dysfunction to minor contribution of oxygen[9].

Therefore, the primary goal of this study was to verify the effectiveness of the use of ECMO in patients with severe acute respiratory failure caused by COVID-19. The secondary objectives were to point out the outcomes of the treatment, side effects, complications and mortality decrease index.

Materials and Methods

Sample and type of study

The following databases were used: Cochrane Library, PubMed (US National Library of Medicine Nation alI Institutes of Health), COCHRANE LIBRARY, EMBASE e CINAHL, utilizando os descritores controlados (DeCS- Descritor de Ciência da Saúde): ("Extracorporeal Membrane Oxygenation*" OR ECMO OR "Extracorporeal Life Support*" OR ECLS) AND ("COVID*" OR Coronavirus OR "SARS*"). For the word combination, the boolean operator "AND". The data used for the searches was from the beginning of the bases until 2020-07-13, when the search was carried out.

The search with the key terms in the databases was conducted by one of the authors. The initial gathering of the articles filtered in doubles (AA and DJ) to conclude the process of selection and eligibility criteria of it. In case of disagreements, a third evaluator (DN) was consulted to reach a consensus.

Delineation of research

It was elaborated a systematic review using the PICO (Patient, Intervention, Comparison and Outcome) intervention to formulate the clinical question of this study, being it:

- Patients: Patients with severe acute respiratory failure caused by COVID-19;
- Intervention: Treatment with use of ECMO;
- Comparison: Severe patients that were treated with the support of ECMO, in comparison to the ones that didn't received this resource;
- Outcome: Effectiveness of the treatment with ECMO.

  With that, a question was formulated: What is the effectiveness in using ECMO during the clinical management of the patients with severe acute respiratory failure caused by COVID-19?

Criteria of Inclusion and Exclusion

All of the articles selected in the databases detailed above, that respected the criteria of inclusion, were included: 1- Papers published in integrality; 2- That have as an objective to evaluate the effectiveness of the treatment of patients with COVID-19 using ECMO; 3- Clinical trials held with individuals diagnosed with COVID-19. There was no restriction by language of publication of the included articles.

Articles that were abstracts, editorials, congress resumés and study protocols, were excluded from this systematic review, such as the articles that did not fulfill the inclusion criteria described above.

Procedures

Initially, the triage was conducted by title and abstract. The selected articles of this triage were read with the complete writing of the article. The extraction of the data was held by the complete reading of the studies, being them:

- Effectiveness of the treatment;
- Treatments outcomes;
- Side effects and complications;
- Mortality decrease index.

Data analysis

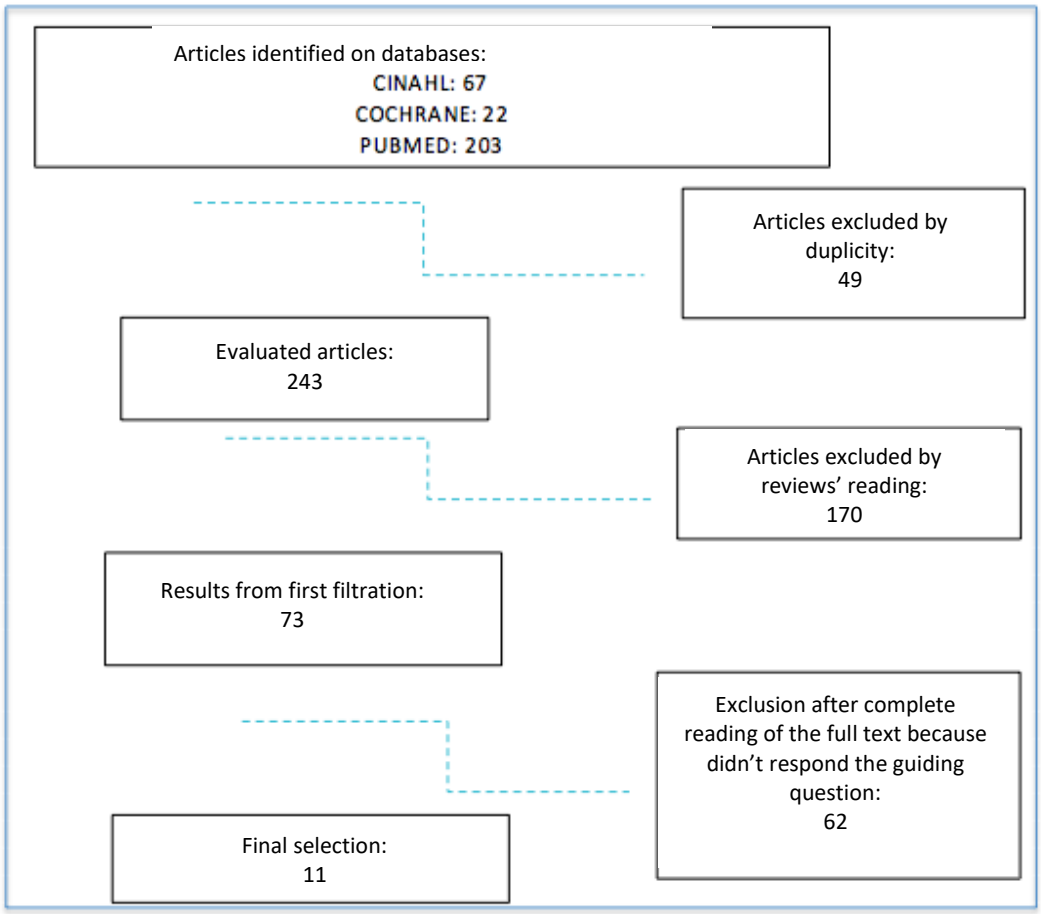
It was not possible to evaluate the methodological quality of the included

studies since it's about heterogeneous designs. Moreover, the results were presented in a descriptive way due to the diversity of obtained data. The collected data were in number, percentage, rate and standard deviation.

Results

Two hundred and forty three articles were identified using the descriptor mentioned before. However, having finished all of the process of selection detailed on the section 'Materials and Methods' of this study, there were only eleven studies left. The Picture 1 illustrates the process of articles selection:

Figure 1. Article selection flowchart.



The Table 1 summarizes the amount of articles found in each database consulted, in absolute numbers and in percentage. Being the majority of database articles PubMed.

Table 1. Absolute numbers and percentages of the articles found on the databases (n=281) consulted in this study.

Databases	**Total number of trials (n=292)**		**Number of articles after the criteria application of inclusion and exclusion (n=11)**	
	N	%	N	%
CINAHL	67	22,94	0	00,0

Cochrane	22	7,53	0	00,0
PubMed	203	69,52	11	100,0%

All of the articles were published in the english language, of which 54,4% were developed in the European Continent. In terms of publication year, 100% of the articles were published in 2020 in different periodicals as described in the Table 2.

Table 2. Author, year, country, periodical and language of the articles included in this study.

Author	Year of Publication	Periodical	Country
Beyls B *et al*[10].	2020	British Journal of Anaesthesia	France
Falcoz PE *et al*[11].	2020	American Journal of Riratory and Critical Care Medicine	France
Haye G *et al*[12].	2020	Journal of Cardiothoracic and Vascular Aneshesia	France
Huette P *et al*[13].	2020	Canadian Journal of Anesthesia	France
Liu J *et al*[14].	2020	Medicine	China
Loforte A *et al*[15].	2020	Asaio Journal	Italy
Marullo A *et al*[16].	2020	Minerva Cardioangiologica	Italy
Osho AA *et al*[17]	2020	Annals of Surgery	USA
Sultan I *et al*[18].	2020	Journal of Cardiac Surgery	USA
Yang X *et al*[19].	2020	Critical Care Medicine	China
Xin L *et al*[20].	2020	Asaio Journal	China

The articles presented as a common goal the comparison of clinical outcomes of the patients submitted to ECMO due to respiratory failure caused by SARS-CoV-2. The test totaled 439 patients, having a variation of 6 to 333 patients by study, the average age of the patients was 47, 13 (DP: 7,2) years old.

The respiratory symptoms were reported in all of the studies, being the severe hypoxemia the most recent finding. Concerning the previous comorbidities, the most detected ones were the systemic arterial hypertension and mellitus diabetes. The Table 3 summarizes the main clinical and epidemiological characteristics of the patients.

Table 3. Main clinical and epidemiological characteristics of the patients.

Authors	Trials	Average age	Symptoms	Previous comorbities
Beyls C *et al*[10].	12	62	Severe hypoxemia	N/R
Falcoz PE *et al*[11].	17	56	N/R	Obesity, SAH, MD
Haye G *et al*[12].	8	57	N/R	Smoking, SAH, MD and overweight/obesity
Huette P *et al*[13].	14	N/R	Severe hypoxemia	Kidney disease
Liu J *et al*[14].	6	66	Fever, cough, diarrhea, myalgia	SAH, MD, Valvular disease, liver transplant
Loforte A et al[15].	4	49	Severe respiratory failure	Obesity, SAH, MD
Marulo A *et al*[16].	333	52	N/R	N/R
Osho AA *et al*[17].	6	47	N/R	MD and obesity
Sultan *et al*[18].	10	N/R	High fever, cough, dyspnea, gastrointestinals	SAH, MD, hyperlipidemia, alcoholism, smoking, asthma, obstructive sleep apnea
Yang X *et al*[19].	21	65,5	N/R	N/R
Xin L *et al*[20].	8	64	Severe refractory hypoxemia to invasive mechanical ventilation	SAH, MD, Hyperlipidemia, alcoholism, asthma

Siglas: systemic arterial hypertension (SAH) e meningococcal disease (MD).
*N/R: Not reported

Few studies analyzed the laboratory characteristics of the patients before and during ECMO. Amid those that reported these data was possible to observe the prevalence of lymphopenia and a lactate increase pre ECMO, and lymphocytosis during the ECMO. The Table 4 summarizes all of the laboratory characteristics reported by the authors.

Table 4. Laboratory characteristics pre and during ECMO.

Authors	Main laboratory characteristics pre ECMO	Main laboratory characteristics during ECMO
Beyls C *et al*[10]	Lactate increase, lymphopenia, thrombocytopenia	Thrombocytopenia
Falcoz PE *et al*[11].	N/R	N/R
Haye G *et al*[12]	Lymphopenia, elevated reactive protein C	N/R
Huette P *et al*[13].	Lymphopenia	Lymphocytosis and fibrinogen degradation
Liu *et al*[14].	Lactate, creatinine, total bilirubin, reactive protein C and procalcitonin and thrombocytopenia increase	N/R
Loforte A *et al*[15].	Lymphopenia and neutropenia	N/R
Marulo A *et al*[16]	N/R	N/R
Osho AA *et al*[17].	Lactate, D-dimer and creatinine increase	N/R
Sultan I *et al*[18].	Ferritin and interleukin elevation	N/R
Yang X *et al*[19].	N/R	Leukocytosis, lymphocytosis, monocytosis and D-dimer and creatinine increase
Xin L *et al*[20].	Lactate increase	N/R

*N/R= not reported

Regarding the position of the patients before ECMO, all of them were set in prone postitions. In addition, the majority of the patients received nitric oxide and anticoagulant at some point of the treatment. When analysing the respiratory parameters pre and post ECMO, we observed that in the vast majority of the studies, the ventilatory parameters were better after the ECMO, as it detailedly shows in Table 5.

Table 5. Ventilatory parameters pre and post ECMO.

Authors	VM Parameters pre ECMO	VM Parameters during ECMO	VM Parameters post ECMO
Beyls C *et al*[10]	Current volume: 6.1; Frequency: 30 incursions by minute; PEEP: 14; Plateau pressure: 28; Respiratory pressure: 14; Complacency: 31	N/R	N/R
Falcoz PE *et al*[11].	FIO2 (%): 100; PaO2/FIO2 ratio: (mmHg): 71; SaO2 (%): 90; Total volume (ml/kg predict corporeal weight): 5,9;	SaO2: 97; Total volume: 3,9; Respiratory frequency: 20; PEEP: 12; Plateau pressure: 26; Conduction pressure: 14	PaO2 /FIO2 ratio: 177; PEEP: 10; Plateau pressure: 26; Conduction pressure: 15; Conformity: 29,5; Oxygenation index: 10

	Respiratory frequency: (breaths/min): 31; PEEP (cm of water): 14; Plateau pressure cm of water): 29; Conduction pressure (cm of water): 15; Conformity (ml/cm of water): 26; Oxygenation index (cm of water/mmHg): 29		
Haye G *et al*[12].	Current volume (ml kg 1): amid 4,2-6,5 Frequency (bpm): amid 30-35 PEEP (cm H2O): amidst 10 and 16; Respiratory pressure (cm H20): amidst 9 and 20 Complacency (ml cm H2O 1): 18-33; PaO2/FiO2= amidst 51 and 95	N/R	N/R
Huette P *et al*[13].	(PaO2/FIO2): 76 mmHg; CO2 pressure: 55 mmHg, Complacency: 30 mLmmHg.	PaO2/FIO2: 129 mmHg; Complacency: 29.3 mLmmHg	N/R
Liu J *et al*[14].	PaO2/FiO2 96; PEEP: 11.5; volume: 6.8; current volume: 525; Inhaling pressure: 28.5; Respiratory frequency: 18	N/R	PaO2/FiO2 329,4; PEEP: 5.2; volume: 9,3; current: 650; Inhaling presssure: 20; Respiratory frequency: 15
Loforte A *et al*[15].	Ventilation (L/min): 11,5; Current volume (ml): 607,5); PEEP (cm H2O); FIO2 (%) 95; PaO2 /FIO2: 50,2; Plateau pressure (cm H2O): 31; Conduction pressure (cm H2O): 16; Conformity (ml /cm H2O): 33,5	N/R	Ventilation: of 4,1- 5,1; Current volume (ml): of 280-320; PEEP (cm H2O): of 10-12; FIO2 (%): of 50-60; Plateau pressure (cm H2O): of 18-19; Driving pressure (cm H2O): of 10-11; Conformity: of 33,2-34,1
Marulo A et al[16].	N/R	N/R	N/R
Osho A *et al*[17].	(rating of the 6 patients): Plateau pressure= 27,66 cm H2O; Volume= 5,23 L/min; Gas sweeping flow= 93,33%	N/R	(rating of the 6 patients): Plateau pressure= 25,5 cm H2O; Volume= 4,78 L/min; Gas sweeping flow= 84,16%
Sultan I *et al*[18].	N/R	N/R	N/R
Yang X *et al*[19].	Flow rate: 1.500 rpm and sustained in 4 L / min	N/R	No survivors: had a continuous need of high flow rates. Survivors: the sweeping flow gradually decreased.

Xin L *et al*[20].	(PaCO2/FiO2): amid 54-76	N/R	N/R

*N/R= not reported

About the outcomes and side effects presented by the patients, it was observed that the days of hospitalization varied from 4 to 60 days, the main complications found were bleeding, thrombotic events and renal alterations. At last, about the mortality, there was a considerable variation between the studies, with a report of 0% of mortality to 51,14%, as the Table 6 shows.

Table 6. Outcomes presented by the analyzed stuydies.

Authors	Hospitalization days average	Outcomes and side effects	Complications
Beyls C *et al*[10].	24	ICU discharge: 67%; Mortality: 33%	Thrombotic complications during cannula insertion; peripheral venous thromboembolism; hypercoagulability state in patients with elevated concentration of reactive protein C
Falcoz PE *et al*[11].	N/R	Hospital discharge: 58,5%; Mortality: 35,3%	Hemorrhage; cardiac tamponade; stroke; pulmonary thromboembolism; thrombosis; pneumonia associated with mechanical ventilation; need of kidney replacement therapy; gas embolism
Haye G *et al*[12].	N/R	ICU discharge: 50%; Need of new ECMO: 12,5%; Mortality: 25%; ECMO maintenance: 12,5%	Bleeding; cannula infection
Huette P *et al*[13].	N/R	ICU discharge: 67%; Mortality: 42,85%	Thrombotic events, pulmonary embolism and need of kidney replacement therapy
Liu J *et al*[14].	22	(after 28 days) Remained on mechanical ventilation: 52%; Remained on ICU: 56%; Transference to infirmary: 22%; Hospital discharge: 22%	N/R
Loforte A *et al*[15].	4	Death or survival	Severe gastrointestinal bleeding

Marulo A *et al*[16].	N/R	Higher risk of death on elderly (p=0,002); Mechanical ventilation weaning: 18,1%; Mortality: 17,1%	N/R
Osho A *et al*[17].	17	Survived the hospital discharge 1: 17%; Survived the decannulation: 67% Mortality with ECMO: 17%; Remained in ECMO: 17%	Acute kidney lesion; bleeding; sepsis; kidney replacement; cerebral vascular accident (CVA)
Sultan I *et al*[18].	18	Cure: 20%; Remained hospitalized until end of research: 10%; Mortality: 10%	Acute kidney injury
Yang X *et al*[19].	N/R	Mortality reduction (without ECMO 63,2% versus with ECMO 57,1%; p = 0,782)	Bradycardia; local bleeding; brain hemorrhage; acute kidney lesion
Xin L *et al*[20].	60	Mortality: 50%; Therapeutic success: 37,5%; Remained in ECMO: 12,5%	N/R

N/R: Not reported

Discussion

The main results of this systematic review showed that the studies trial was predominantly elderly and had as main base diseases arterial systemic hypertension (ASH), meningococcal disease (MD) and obesity[10-20]. Concerning the laboratory characteristics, an increase of the lactate level[10,14,17,20], lymphopenia and increase of the reactive protein C[12,14] can be predominantly observed. Researchers[21,22] emphasized that the patients with COVID-19 that evolved to the more severe form of the disease, had the same risk factors found in this study, as well as the same laboratory alterations, as described by Rajagopal and collaborators[23].

In terms of side effects, it's worthwhile to remember that the definition of side effect it's: every harmful or unwanted reaction that occurs during or after an intervention or the use of a medication[22,24]. Therefore, the possible side effects associated with the use of ECMO were blood alterations, such as thrombocytopenia[10], fibrinogen[13] degradation and bradycardia[19]. About the complications, defined as unfavourable evolutions in spite of an instituted treatment, from the eleven studies analyzed, nine reported some kind of complication. Among them, the bleedings stood out, both at the puncture site, and in various organs as the brain and gastrointestinal system[10,11,15,17,19], thromboembolic events, kidney injury[11,13,17,18,19], infection at the puncture site[11], aside the pneumonia associated to mechanical ventilation[11 13]. In contradiction, an abstract was held by Savarimuthu et al. 2020[23] also reported that the main complications located on the patients on ECMO were hemorrhages, both at the puncture site and in other organs, such as the brain, besides of thromboembolic events, infections and pneumonia associated to mechanical ventilation[23].

On the other hand, the mortality ranged considerably from a study to another, the lower mortality rate being equal to 0%[14] and the highest equal to 57,14%, such variation can be explained by the sample size in the studies, complexity of the patients and clinical handling of a disease with uncertain and minimally known evolution, as well as by the service experience with the use of ECMO. From the analyzed studies, only one reported mortality decline of 63,2% to 57,1% (p=0,782)[19]. Haiduc et al[26]. also observed a reduction of the mortality rate on the patients that used ECMO.

Additionally, it was noticed that ECMO has been used as retrieval therapy to patients with acute respiratory failure caused by SARS-CoV-2[21], with that, several researches are describing their experience with this therapeutic strategy, nevertheless, it was possible to observe, by this systematic review, that the majority of the publications were non clinically tested articles as commentary, letter to editor, editorials, etc. Therefore, there's a diminutive number of studies that followed and/or compared the patients that used this therapy to those that didn't receive the treatment with ECMO. Consequently, it is suggested that new trials are made to confirm the obtained results of this study.

Conclusion

In conclusion, the patients that needed ECMO were predominantly elderly who had as risk factors systemic arterial hypertension (SAH), meningococcal disease (MD) and obesity. The main complications found were bleeding and thromboembolic phenomenons. Ultimately, the mortality rate ranged considerably among the studies, being noticeable a possible reduction of the mortality rate amid patients that were submitted to this treatment. However, by being a recently studied health condition, it is necessary that new studies are conducted to confirm the efficacy of ECMO on patients with COVID-19.

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