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REVIEW ARTICLE

Extracorporeal Membrane Oxygenation use on Liver Transplantation: An Integrative Review

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ABSTRACT

Objective: To review the applicability of extracorporeal membrane oxygenation (ECMO) during the pre, intra and postoperative periods of patients undergoing liver transplantation. **Methods:** This is an integrative review that seeks to evaluate the indications for the use of ECMO in liver transplantation. As databases, were used: MEDLINE, Web of Science and Scopus, with articles published in the last ten years in English and Portuguese. **Results:** In this review, 24 papers were included, of which 3 were original articles and 21 were case reports. The studies were divided according to the ECMO application period concerning the liver transplant: one for the preoperative, eight intraoperative and 15 postoperative. It was identified that ECMO use is mainly related to hepatopulmonary syndrome complications. The limited number of studies regarding using ECMO in the preoperative period reflects the importance of hepatic transplant as the main measure to manage liver disease complications. In the intraoperative phase, ECMO usage is expressive in managing cardiopulmonary complications refractory to previous interventions. The use of this mechanism in the postoperative period is the most reported. The main indication is severe hypoxemia secondary to hepatopulmonary syndrome, in which other treatments have been ineffective. The main complications related to this mechanism were sepsis, renal failure and bleeding. **Conclusion:** ECMO is an important therapeutic modality for managing complications resulting from liver transplantation. However, only some studies in the literature have an adequate sample number to assess its actual efficacy and level of safety.

Descriptors: ECMO; Liver transplant; Perioperative period; Hepatopulmonary syndrome; Sepsis.

Uso de Oxigenação por Membrana Extracorpórea no Transplante Hepático: Uma Revisão Integrativa

RESUMO

Objetivo: Revisar a aplicabilidade da Oxigenação por Membrana Extracorpórea (ECMO, do inglês *extracorporeal membrane oxygenation*) durante os períodos pré, intra e pós-operatório de pacientes submetidos ao transplante de fígado. **Metodologia:** Trata-se de uma revisão integrativa que buscou avaliar as indicações do uso da ECMO no transplante hepático, assim como suas complicações. Utilizou-se as bases de dados: MEDLINE, Web of Science e Scopus, com artigos publicados nos últimos 10 anos, em inglês e português. **Resultados:** Nesta revisão foram incluídos 24 trabalhos, dos quais 3 eram artigos originais e 21 eram relatos de caso. Os estudos foram divididos de acordo com o período da aplicação da ECMO em relação ao transplante hepático: 1 em relação ao pré-operatório, 8 ao intraoperatório e 15 no pós-operatório. Identificou-se que o uso da ECMO possui como principal indicação complicações relacionadas à síndrome

hepatopulmonar. A quantidade limitada de artigos com uso na ECMO no pré-operatório reflete a importância do transplante hepático como principal medida para manejo das complicações da doença hepática. Na fase intraoperatória, a utilização da ECMO é expressiva no manejo de complicações cardiopulmonares refratárias a intervenções prévias. O uso desse mecanismo no pós-operatório identifica-se como o mais relatado, com principal indicação na hipoxemia grave secundária à síndrome hepatopulmonar em que outros tratamentos foram ineficazes. As principais complicações relacionadas ao uso do dispositivo foram sepse, falência renal e sangramento. **Conclusão:** A ECMO é uma modalidade terapêutica importante para o manejo de intercorrências provenientes do transplante hepático. Todavia poucos estudos na literatura possuem um número amostral adequado para avaliar sua real eficácia e seu nível de segurança.

Descritores: ECMO; Transplante de Fígado; Período Perioperatório; Síndrome Hepatopulmonar; Sepse.

INTRODUCTION

Liver transplantation was first applied in 1963 by Startz *et al.* and is under constant study to ensure the best prognosis for patients undergoing this treatment.[1] Among the actions developed around transplantation is the management of pre- to postoperative complications, including heart failure, severe respiratory failure, and other systemic syndromes, which require alternative therapies.[2] Extracorporeal membrane oxygenation (*ECMO*) is a therapeutic modality that ensures gas exchange, mechanical ventilation, and support for systemic and pulmonary blood flow. This oxygenation ensures assistance for situations of respiratory and cardiac failure,[3] becoming increasingly frequent in the treatment of diseases associated with liver transplantation.[4]

The literature points to the use of ECMO during the intraoperative period, in cases of severe post-reperfusion syndrome,[5] and postoperatively in cases in cases such as respiratory distress syndrome from persistent or remnant hepatopulmonary syndrome.[6] However, its use is not yet well established,[4] with a controversial literature about its indications. In this context, some studies show complications, such as sepsis and bleeding, that make it even more difficult to weigh the benefits against the risks of this clinical conduct.[5–7]

Given this, this review aims to evaluate the indication of ECMO during the pre-, intra-, and postoperative periods of liver transplantation.

METHODS

This study is configured as an integrative review, which used the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA)[8] protocol to analyze the indications of ECMO in the patient in the pre-, intra- and postoperative liver transplantation. The initial discussion focused on the topic "liver transplantation", reached through the FINER *(*Feasible, Interesting, Novel, Ethical, and Relevant) method,[9] to raise a current technique and to generate a discussion regarding the benefits of its application in patients during such a procedure. The elements of the PICO method were then established (Table 1).[10]

Table 1. Elements of the PICO method.

Acronym	Definition	Description
P	Patient or problem	Adults in perioperative liver transplantation, without restrictions of sex, age or ethnicity
I	Intervention or topic of interest	Use of ECMO
C	Control or comparison	No use of ECMO
O	Outcome or results	Decreased mortality rate

Thus, the guiding question for this study was elaborated: "Is the use of ECMO in perioperative adult liver transplantation a factor in reducing mortality when compared to not using this tool?"

The databases that cover the largest amount of evidence about the research problem were used, among them: MEDLINE, Web of Science, and Scopus. The search was performed targeting articles on adults in the pre-, intra-, and postoperative periods of liver transplantation in which ECMO was a necessary therapeutic modality for the management of complications of liver disease, eliminating the pediatric population and other pathologies with an indication for ECMO, such as COVID-19. All sources were last consulted on August 24, 2022. The review was not registered.

- MEDLINE: ((Liver_Transplantation[Title/Abstract]) AND (ECMO OR Extracorporeal Membrane Oxygenation[Title/Abstract])) AND (("2012/01/01"[Date - Publication] : "3000"[Date - Publication]))
- Web of Science: ((TS=(Liver_Transplantation) AND TS=(ECMO OR Extracorporeal_Membrane_Oxygenation) AND PY=(2012-2022))

- Scopus: (TITLE-ABS-KEY (liver_transplation) AND TITLE-ABS-KEY (ecmo OR extracorporeal_membrane_oxygenation)) AND PUBYEAR > 2011 AND PUBYEAR > 2011

Regarding the inclusion criteria, original articles in English and Portuguese, published in the last ten years, and with procedures performed in individuals over 18 years old were included. The criteria used for exclusion were articles with inadequate study type, such as a letter to the reader, editorial, reviews and congress annals; articles focused on the pediatric population; articles that were not related to the central objective of the review, that is, those that discussed other diseases parallel to liver diseases or that did not exclusively discuss liver transplantation, such as simultaneous transplants. Case reports were included, even with the low level of scientific evidence, since the number of original articles was limited, compromising the review.[2,6,11–13] The *Critically Appraised Topic (CAT) Manager App* was used to assess the risk of study bias. The following limitations were identified: the presence of a nonrandomized study and the presence of studies without the possibility of evaluating effect measures.

The Rayyan online platform was used to select the studies according to the PRISMA 2020 Flow Diagram. The platform provides an automatic filtering tool for duplicate articles; in addition, the filtering was done independently among reviewers through the *blind mode* function, which makes it impossible for one reviewer to see the exclusion and inclusion decision of the other editors, decreasing the risk of bias. Articles were selected by at least two reviewers at initial filtering from abstract and title reading. A third party evaluated the tie-breaking criteria in case of disagreement between the reviewers' decisions. In the full-text reading stage, the 24 articles included were divided among the reviewers and evaluated independently, and their data were extracted and summarized in the attached tables. For data extraction, the following information was sought: year, method, condition that indicated the use of ECMO, time of transplantation when ECMO was used (pre-, intra- and postoperative), complications associated with the use of ECMO, and death. In case series and retrospective studies, the number of patients and the number (absolute or relative) of patients associated with each complication were specified.

RESULTS

Twenty-four articles were included, of which 3 were original, and 21 were case reports. The studies were divided according to the period of ECMO application in relation to liver transplantation: 1 preoperatively, 8 intraoperatively, and 15 postoperatively (Fig. 1).

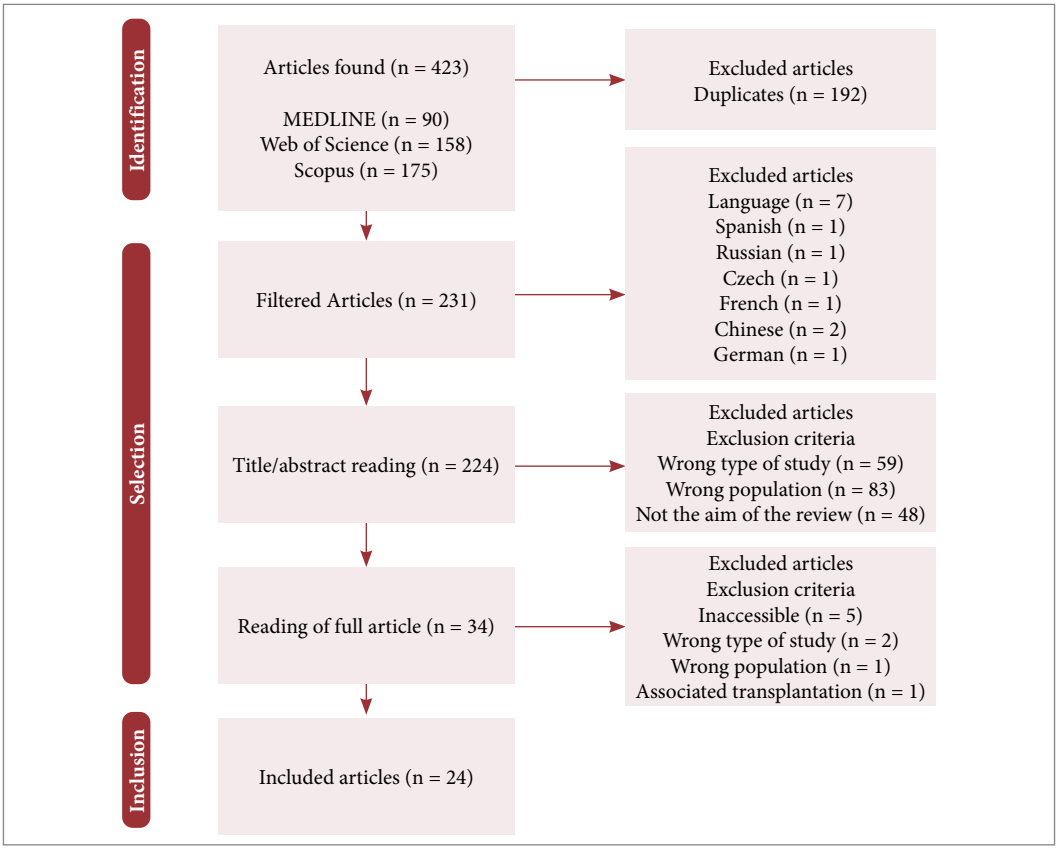

Figure 1. Flowchart of the article selection process.

Preoperative

The only article addressing preoperative ECMO demonstrates the use of the device to stabilize severe portopulmonary hypertension (Table 2). In this case, there were two attempts to perform liver transplantation, but the patient could not tolerate general anesthesia and was refractory to using vasopressors. ECMO was used as a strategy to avoid this systemic imbalance and proved to be efficient for this, ensuring the execution of the operation without causing direct complications.[7]

Table 2. Indications of ECMO in preoperative liver transplantation.

Article	Type of study	Indication	Complications	Number of individuals
Barbas *et al.* (2021)[7]	Case report	Severe pulmonary hypertension	Acute renal failure	1

Intraoperative

Eight articles indicated the use of intraoperative ECMO, with two major subgroups as indications: the repercussion of previously diagnosed conditions or complications after severe post-reperfusion syndrome (Table 3).

Table 3. Indications of ECMO in intraoperative liver transplantation.

Article	Type of study	Indication	Complications	Number of individuals
Voulgarelis *et al.* (2021)[5]	Case report	Cardiac arrest due to hypovolemia with asystole	Pulmonary hemorrhage	1
Chou *et al.* (2020)[12]	Retrospective cohort study	Cardiovascular and respiratory pathologies.	-	42
Sun *et al.* (2018)[14]	Case report	Heart failure and pulmonary hypertension.	-	1
Martucci *et al.* (2017)[15]	Case report	Post-reperfusion cardiac arrest.	Sepsis, multiple organ failure. Death	1
Van Hoof *et al.* (2021)[16]	Case report	Hyperkalemic cardiac arrest.	Intraoperative hyperkalemic cardiac arrest	1
Tejani *et al.* (2015)[17]	Case report	Ventricular fibrillation after hepatic reperfusion.	Post-reperfusion ventricular fibrillation of the liver.	1
Romano *et al.* (2021)[18]	Case report	Heart failure secondary to post-reperfusion intracardiac thrombosis.	Sepsis, multiple organ failure. Death	1
Eudailey *et al.* (2015)[20]	Case report	Post-reperfusion cardiogenic shock.	-	1

Sun *et al.* cite the use of ECMO in patients with severe cardiocirculatory dysfunction to alleviate the stress caused during transplantation.[14] Whereas Martucci *et al.* cite portopulmonary hypertension as an eligible condition of its use.[15] Other situations, such as occlusion of important veins in circulatory drainages, such as the brachycephalic, internal jugular, and subclavian veins, have also been evaluated for using ECMO.[5] As for cases of hemodynamic repercussion due to severe post-reperfusion syndrome, six articles reported the issue, with two papers about cardiac arrest,[15,16] while others showed arrhythmia,[17] intracardiac thrombosis,[18] severe pulmonary embolism,[19] and cardiogenic shock.[20] In four of them, cardiopulmonary resuscitation maneuvers with vasoactive drugs were performed, however, without success.[16–18,20] In these, cardiac rhythm resumed after using ECMO, with no major associated complications developed. In another case, cardiac resuscitation was successful before installation, but the patient developed septic shock postoperatively, and died.[15] As for the case of severe pulmonary embolism, the patient had a shock, requiring vasopressors for hemodynamic control, and improvement in systemic pressure after using ECMO, without developing complications.[19]

In addition, Chou *et al.* demonstrated in a nationwide retrospective cohort study done in Taiwan the use of ECMO in perioperative, involving cases from the intra- and postoperative periods. The National Health Plan Database (*NHIRD*) was used to compare the mortality of patients with liver cirrhosis undergoing the use of ECMO, with people without liver cirrhosis undergoing ECMO, from 2000 to 2013. Of the 7,003 patients analyzed, 233 had liver cirrhosis, and of these, 42 underwent liver transplantation and underwent ECMO; 84.2% of patients with liver cirrhosis who used ECMO and did not undergo transplantation died within two years. Mortality among liver transplant patients is even higher: of the 27 patients who underwent ECMO during the intraoperative period of transplantation, 25 died within two years of admission, and of the 15 who underwent ECMO postoperatively, 14 died within two years.[12]

Postoperative

ECMO is widely referenced in the postoperative period, as exemplified in 62.5% of the reviewed articles (15 articles in total) (Table 4). Included in these studies were eleven case reports,[11,13,21–25] two case series[19,26] and two original articles,[2,6] in which the main

indications were severe respiratory syndromes and cardiovascular conditions. Among the studies in this scenario, six addressed remnant hepatopulmonary syndrome[11,19,23–26] and six dealt with secondary respiratory distress syndrome.[6,19,21–23,26] ECMO was also present in scenarios of cardiovascular failure when the use of medications, mechanical ventilation, and other conventional treatments proved ineffective; one reported two cases of thrombus,[19] one addressed severe pulmonary embolism and cardiac arrest,[26] one discussed cardiogenic shock,[26] one portal vein thrombosis[25] and one pulmonary congestion.[27] Furthermore, its use was also frequent as a treatment protocol for septic shock, established in 3 of the 14 articles analyzed;[2,13,22] however, these scenarios were generally accompanied by respiratory insufficiencies.

Table 4. Indications of ECMO in the postoperative period of liver transplantation.

Article	Type of study	Indication	Complications*	Number of individuals
Lee *et al.* (2017)[2]	Retrospective study	Refractory septic shock.	-	8
Seo *et al.* (2015)[6]	Retrospective study	Severe acute respiratory distress syndrome.	Septic shock. Death.	32
Gagnon *et al.* (2018)[11]	Case series	Severe secondary hypoxemia as a consequence of post-transplant hepatopulmonary syndrome. Subsequently, refractory hypoxemia.	-	1
Gedik *et al.* (2015)[13]	Case series	Acute respiratory failure and sepsis	Refractory septic shock (1). Multiple organ failure (1). Death (2).	2
Goussous *et al.* (2019)[19]	Case series	VV-ECMO (4): ARDS (3) and persistent hepatopulmonary syndrome (1) | VA-ECMO (4): circulatory collapse due to thrombus in the right ventricle	Decannulation failure (1); renal failure (6); severe internal bleeding (4); need for tracheostomy (6)	7
Scheckley *et al.* (2022)[21]	Case report	Disseminated intravascular coagulation and ARDS secondary to TRALI.	-	1
Park JI *et al.* (2017)[22]	Case report	Septic shock from aspiration pneumonia.	-	1
Stratta *et al.* (2013)[23]	Case report	Portopulmonary hypertension, ARDS.	-	1
Geevarghese *et al.* (2017)[24]	Case report	Hypoxemia secondary to hepatopulmonary syndrome.	-	1
Piltcher-da-Silva *et al.* (2022)[25]	Case report	Hypoxemic respiratory failure due to hepatopulmonary syndrome.	Bleeding and edema of the liver.	1
Braun *et al.* (2019)[26]	Case series	VV-ECMO (4): ARDS - hypoxemic respiratory failure (1), hepatopulmonary syndrome - hypoxemic respiratory failure (2) and inferior vena cava mechanical obstruction - chronic venous insufficiency (1) | VA-ECMO (4): heart failure (3) and pulmonary embolism (1)	Decannulation failure (4); multiple organ failure (1). Death (5)	8
Yoo *et al.* (2013)[27]	Case report	Severe hypoxia secondary to pulmonary congestion and edema.	Sepsis, multiple organ failure. Death	1
Lauterio *et al.* (2022)[31]	Case report	Dyspnea and severe hypoxemia due to pulmonary edema, electrocardiographic changes, and ventricular systolic dysfunction.	-	1
Kumar *et al.* (2017)[34]	Case report	Hypoxemic respiratory failure due to hepatopulmonary syndrome.	-	1

*In case of a study with more than one patient, the absolute number of patients per complication was specified. **ECMO: extracorporeal membrane oxygenation; VV-ECMO: venovenous ECMO; VA-ECMO: venoarterial ECMO; ARDS: acute respiratory distress syndrome; TRALI: transfusion-related acute lung injury.

When it came to the complications of these types of ECMO applications, two of the eleven reports showed severe complications directly related to the support technique.[13,27] Among the case series, it was reported by Goussous *et al.* that one of seven patients could not be decannulated, five patients suffered with renal failure, and four patients demanded to be reoperated because of severe internal bleeding. All patients who were decannulated required tracheostomy and two patients died in the hospital from fungemia and respiratory failure and one died from conditions parallel to ECMO;[19] Braun *et al.* reported that there were cases of renal failure, bacteremia, and tracheostomy, and only three of the eight patients survived.[26]

Furthermore, Seo *et al.* discuss in their article ECMO use in acute respiratory distress syndrome (*ARDS*), aiming to study the use of the device in patients who had been refractory to the other established treatments. A total of 69 patients were observed, reaching a survival rate of 18.8%, of whom 35 died while using ECMO.[6] Lee *et al.* published a retrospective study that aimed to analyze the use of ECMO in cases of septic shock after ineffective conventional treatment. Eight individuals were studied, of

whom two survived and did not suffer direct complications from ECMO. This article concluded that this therapeutic modality could be used as rescue therapy for patients with refractory septic shock, with a survival rate of 25%.[2]

DISCUSSION

ECMO can be used for complications secondary to liver transplantation, especially cardiopulmonary failure.[23] Two modalities of ECMO are currently employed, the venovenous ECMO (VV-ECMO) and venoarterial ECMO (VA-ECMO), the latter being involved with maintaining the patient's hemodynamic balance and supporting lung function, which is the basis of this cardiopulmonary therapy.[6] ECMO has a 30–40% survival rate in patients with unfavorable survival prognoses, such as in severe hepatopulmonary syndrome, its main indication in this context.[28] This condition involves the simultaneity of severe hypoxemia and advanced liver disease, causing systemic failure that can sometimes be refractory to conventional treatment, requiring ECMO intervention as a last resort.[29]

Of the 24 selected articles, only 1 addressed the indication of ECMO in the preoperative period. It is known that this therapeutic modality is of great complexity, being considered an invasive procedure, generally used after other conventional treatments have proven ineffective.[30] Thus, the indication of the technique requires careful consideration of the risks based on well-structured protocols and a study of the specific case. An example of this was the article by Barbas *et al.*, in which VV-ECMO was employed to ensure patient survival to liver transplantation. In this case, the patient had severe portopulmonary hypertension, and two transplant attempts were aborted due to hemodynamic instability after induction of anesthesia. The installation of preoperative ECMO was necessary for the gradual improvement of lung function and, ultimately, conduction to surgery.[7]

ARDS and hepatopulmonary syndrome were the most frequent conditions justifying the use of ECMO after liver transplantation.[6,11,14,19,20,22–24,31] ECMO has been initiated in patients in whom liver transplantation was insufficient to recover respiratory function, and respiratory support was necessary to resolve severe hypoxemia secondary to remnant hepatopulmonary syndrome.[6] From this perspective, ECMO emerges as the *bridge to the decision*, that is, it ensures the stabilization of the patient from their serious condition and enables the careful evaluation of the case to plan the next steps of treatment. This strategy was seen frequently during the SARS-CoV-2 pandemic, during which this therapeutic modality was widely employed in patients with severe lung damage.[23,26,32,33]

Although ECMO is an important source of support for treating cardiorespiratory complications in liver transplantation, it is still an invasive and unconventional treatment with high risk.[12] The device is considered quite controversial, as it can often lead to unfavorable repercussions such as septic shock,[13,18] excessive intraoperative bleeding,[5] infection,[21] renal failure,[19,31] heart failure[31] and internal bleeding.[19,34] Due to the intrinsic risks, the therapeutic modality is a treatment of the last choice and should be carefully evaluated as to its necessity.[35] Seo *et al.* presented data on the treatment of ARDS by ECMO, with survival rates in this scenario below 20%.[6] Chou *et al.,* on the other hand, described a 92.6% mortality rate. Since it is a last-line treatment, it is difficult to distinguish between deaths resulting from ECMO and deaths that occurred due to the severity of the liver disease, in which the intervention did not influence the evolution.[2,6,12,13,18,19,29,31]

It is clear that a large number of case reports compromises the level of evidence of the article, due to the impossibility of evaluating measures of effect. However, the use of ECMO for the management of complications of liver disease is a recent therapeutic modality, with few published studies of impact and adequate sample size.

CONCLUSION

It is concluded that ECMO can be a useful therapeutic modality for managing various scenarios in the pre-, intra- and postoperative period of liver transplantation. However, due to its risks, a measured use of this cardiopulmonary therapy is necessary, since it is associated with several complications, such as bleeding and sepsis. More studies of the use of ECMO during this period are needed to create more detailed protocols to ensure that the application is effective and safe.

CONFLICT OF INTEREST

Nothing to declare.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silva HRS, Costa LRO and Fonseca Neto OCL; **Conception and design:** Costa LRO, Zoby HN, Falcão LBOA, Correia LCB, Rêgo MVAS, Wanderley GV, Vilachan FPG, Lima CVO, Silva HRS and Fonseca Neto OCL; **Data analysis and interpretation:** Zoby HN, Falcão LBOA, Correia LCB, Rêgo MVAS, Wanderley GV,

Vilachan FPG and Lima CVO; **Article writing:** Costa LRO, Zoby HN, Falcão LBOA, Correia LCB, Rêgo MVAS, Wanderley GV, Vilachan FPG and Lima CVO; **Critical review:** Costa LRO and Fonseca Neto OCL; **Final approval:** Fonseca Neto OCL.

AVAILABILITY OF RESEARCH DATA

All data sets were generated or analyzed in the current study.

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