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REVIEW ARTICLE

Retrograde Reperfusion in Liver Transplantation: An Integrative Literature Review

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ABSTRACT

Introduction: liver transplantation is a complex process, which has controversies about which reperfusion technique is the most suitable to minimize the damage caused by ischemic injury. There is no consensus on a technique of reperfusion of primary choice in the evidence found. Therefore, we can´t reach a conclusion. **Purpose:** this study aims to investigate the scientific production of retrograde reperfusion and its implication in liver transplants. **Method:** integrative review of the literature, developed through searches in the PubMed, Scielo, and Lilacs Databases. After the analysis and application of the inclusion and exclusion criteria defined by the authors, we selected 6 published articles to write this review, without restricting the dates of publication. **Results:** Retrograde revascularization during liver transplantation seems to be a correct option for reducing intrasurgical complications and decreasing graft ischemia time, in addition to having no significant disadvantage that justifies the non-use of the technique during the procedure. The major limitation of the studies included in the review was the small number of liver transplants in which the technique was used, since there is a preference for anterograde revascularization, mainly portal. **Conclusion:** retrograde reperfusion proved being efficient in reducing toxic metabolites and post-reperfusion syndrome, in addition to having a certain influence on hemodynamic stability and a lower incidence of graft loss due to primary dysfunction. However, it is necessary to develop new studies that can prove the repercussions of this technique.

Keywords: Retrograde Reperfusion; Liver Transplant; Revascularization.

Reperfusão Retrógrada no Transplante de Fígado: Uma Revisão Integrativa da Literatura

RESUMO

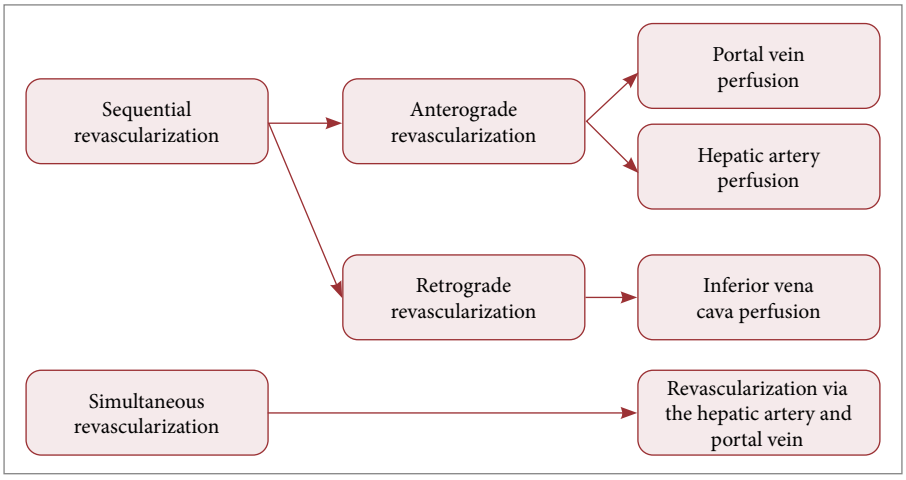
Introdução: o transplante de fígado é um processo complexo, o qual possui controvérsias sobre qual a técnica de reperfusão é a mais adequada para minimizar os danos gerados por lesão isquêmica, não havendo consenso sobre uma técnica de reperfusão de escolha primária. Portanto, este estudo visa investigar a produção científica a respeito da reperfusão retrógrada e sua implicação no contexto do transplante hepático. **Método:** revisão integrativa da literatura desenvolvida por meio de buscas nas bases de dados PubMed, Scielo e Lilacs. Para compor esta revisão, após análise e aplicação dos critérios definido pelos autores, foram selecionados 6 artigos publicados, sem limitação da data de publicação. **Resultados:** a revascularização retrógrada durante o transplante hepático parece ser uma boa alternativa para redução de complicações intraoperatórias e diminuição do tempo de isquemia do enxerto, além de não possuir desvantagem importante que justifique a não utilização da técnica durante o procedimento. A maior limitação dos estudos incluídos na revisão foi a pouca quantidade de transplantes de fígado que utilizam da técnica, já que há preferência pela revascularização anterógrada, principalmente portal. **Conclusão**: a reperfusão retrógrada se mostrou eficiente para reduzir metabólitos tóxicos e síndrome pós-reperfusão, além de possuir certa influência na estabilidade hemodinâmica e na menor incidência de perda do enxerto por disfunção primária. Porém, faz-se necessária a produção de novos estudos que possam comprovar tais repercussões dessa técnica.

Descritores: Reperfusão Retrógrada; Transplante de Fígado; Revascularização.

INTRODUCTION

Liver transplantation is mainly indicated for terminal liver diseases. In 1968, Starzl reported the first successful liver transplants (liver Tx)[1]. Still, since then, surgical techniques have been questioned, investigated, and compared.[2] Therefore, the types of reperfusion used in transplantation are part of these questions. Studies seek the best method to minimize graft injuries and reduce surgical time.

The reperfusion techniques used in orthotopic liver transplantation can be divided into two categories (Fig. 1): sequential revascularizations of the graft, in which it is perfused either through the portal vein or the hepatic artery (anterograde reperfusion) or even through the inferior vena cava (retrograde reperfusion); and simultaneous revascularization, in which there is concomitant reperfusion through the portal vein and the hepatic artery.[3]



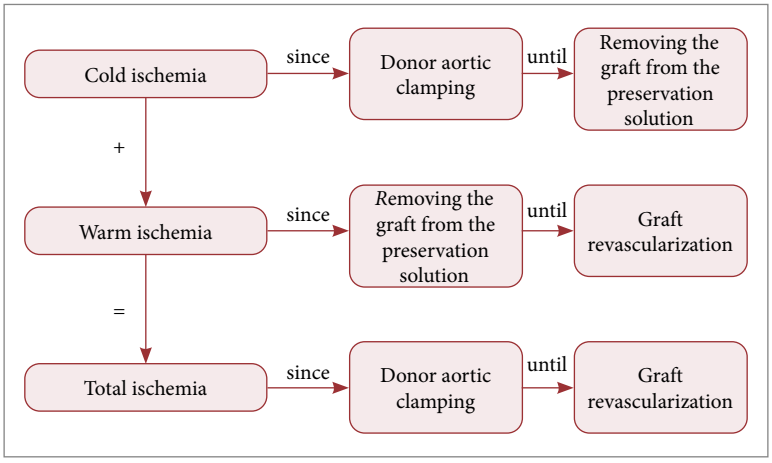
Source: Elaborated by the authors.

Figure 1. Flowchart on reperfusion techniques in liver transplantation.

The graft revascularization step is one of the critical points of liver Tx surgery. Also, several factors are associated with the procedure's success and non-rejection of the organ, including the time of ischemia.[3]

Ischemia time is critical during the procedure, categorized into three types: cold, warm, and total (Fig. 2). The cold ischemia time refers to the interval from the clamping of the donor aorta, if the transplant is from a cadaver donor, until the removal of the graft from the preservation solution.

Warm ischemia time refers to the interval from removing the liver from the preservation solution until the opening of the portal vein anastomosis during implantation of the liver graft in the recipient patient if the revascularization of choice is anterograde- the most frequent method of revascularization. Thus, adding both ischemia times, we have the total ischemia time. Cold ischemia and, mainly, warm ischemia lead to cellular damage,[3,4] impairing the organ's viability.



Source: Elaborated by the authors.

Figure 2. Isquemia times.

Cellular damage

One of the primary functions of the liver is the maintenance of homeostasis, and surgical procedures, such as liver transplantation, can result in injuries caused by ischemia or reperfusion of the graft. In these cases, the injuries result from

changes in hepatic blood flow. The pathophysiology of this type of injury is intertwined with the action of reactive oxygen species produced during reperfusion, which can stimulate the release of pro-inflammatory cytokines, inducing inflammation mediated by neutrophils.[4]

Retrograde reperfusion

During reperfusion of the organ implanted in liver transplantation, hemodynamic instabilities resulting from acid-base disturbances are standard. In this context, different surgical techniques can be considered to prevent and reduce intraoperative complications, mainly Post-Hepatic Reperfusion Syndrome (PHRS).[5]

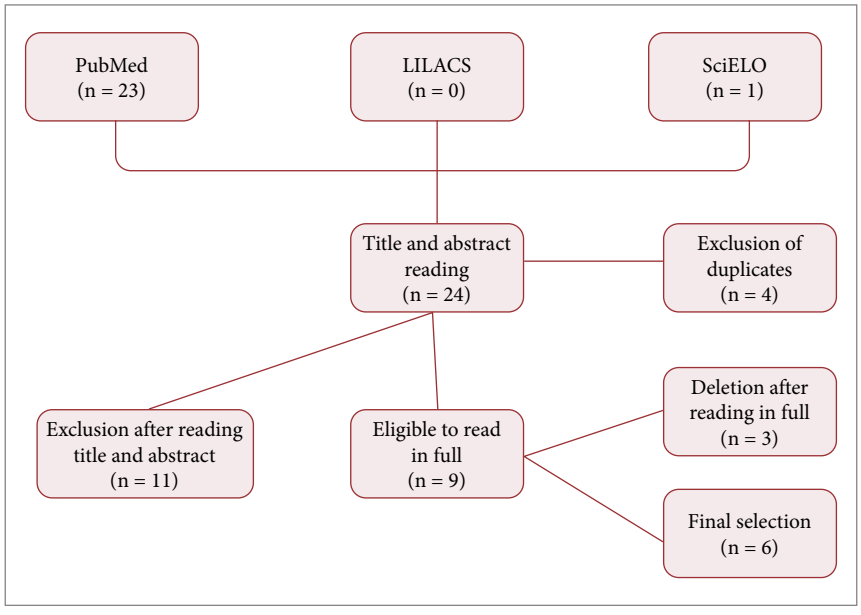
Some studies demonstrate that retrograde reperfusion through the inferior vena cava (IVC) can be an excellent choice to reduce the hemodynamic events during surgery.[5–8]

Unlike the most commonly used method — which revascularizes the liver anterogradely by releasing the portal vein clamping- in this type of reperfusion, revascularization is performed retrogradely by releasing the IVC, either in conventional transplantation or in piggyback, before releasing the portal vein. In this way, blood will reach the liver before the portal vein anastomosis is released.[5–8]

Although studies have investigated the importance of the retrograde reperfusion method in reducing graft injury, there is no established protocol. Therefore, we carried out a literature search for an overview of retrograde revascularization and the implications of this procedure described in the literature.

METHODS

The integrative review (IR) was the method chosen for the present study, conducted with the elaboration of the guiding question, with the search for primary studies in the literature, the evaluation of the studies included in the review, the analysis and synthesis of the results and the presentation of the integrative review[9] (Fig. 3).



Source: Elaborated by the authors.

Figure 3. Flowchart of identification, selection and inclusion of studies in the integrative review.

The guiding question of the IR was based on the PICO strategy, an acronym for Patient (candidates for liver transplantation); Intervention (retrograde reperfusion technique during liver transplant surgery); Control or Comparison (does not apply to the study); and Outcome or Outcome, resulting in the following question: what evidence is available in the literature on performing retrograde revascularization as a technique in liver transplantation?

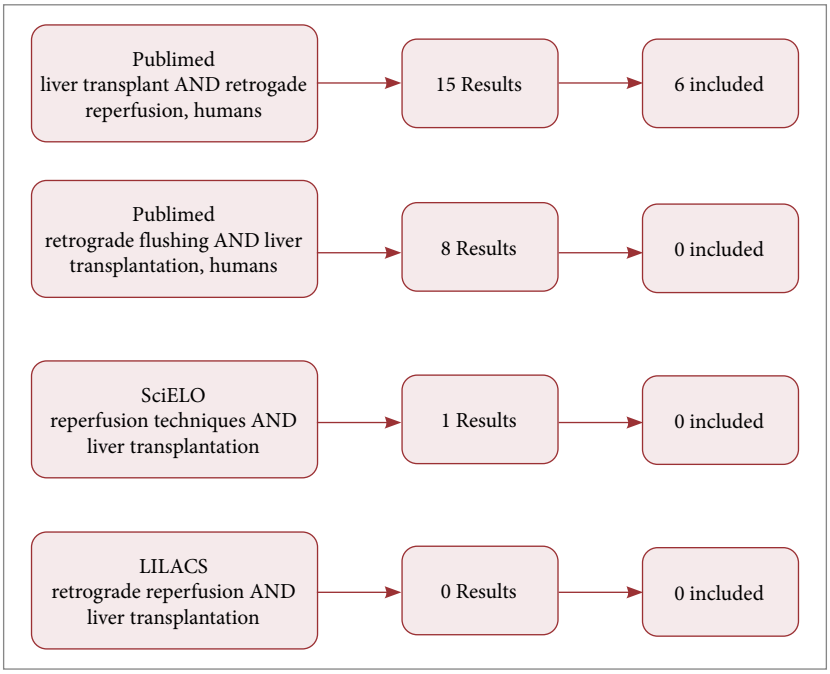
For the bibliographic survey, a search was carried out in the following databases: PubMed — a service of the U. S. National Library of Medicine (NLM); Latin American and Caribbean Literature in Health Sciences (LILACS); and Brasil Scientific Electronic Library Online (SciELO). The following descriptors and their combinations in Portuguese and English were used to search for articles in the literature:

"*Transplante hepático*", "*Reperfusão retrógrada*", "Liver transplant", "Retrograde reperfusion". In addition to these descriptors, articles from the PubMed database were selected using the "humans" filter, and the search for "*Reperfusão retrógrada e Transplante hepático*" did not generate any results in SciELO and LILACS.

The inclusion criteria for selecting articles were: articles published in Portuguese or English, articles in full with the theme referring to the integrative review and articles published and indexed in the referred databases without limitation for the publication date (Fig. 4).

For the first bibliographical selection, the title and abstract were read. Subsequently, the articles were read in full, and those that met the inclusion criteria were attached to the sample of the integrative review.

For data extraction, a script was used, and a table was prepared with the data of each selected study, including data on article identification, location and methodological characteristics.



Source: Elaborated by the authors.

Figure 4. Articles included in this study.

The terminology used by the research authors was adopted to identify the primary studies design. When there was no identification of the type of study, the design analysis was based on the concepts of the specialized literature.

Data analysis and synthesis were carried out descriptively, allowing the reader to summarize each study included in the integrative review and identify the need for future studies on this topic to answer the questions raised here.

RESULTS

Retrograde revascularization during liver Tx is a good alternative for reducing intraoperative complications and decreasing graft ischemia time, in addition to not having a significant disadvantage that justifies not using the technique during the procedure. The major limitation of the studies included in the review was the small number of liver transplants that used the technique since there is a preference for anterograde revascularization, mainly portal (Tables 1 and 2).

Table 1. Characteristics of primary studies according to authors, year, study location, design and authorship.

Authors/Year	Study Location	Outline	Authorship
(E1) Czigany et al. (2018)[6]	International	Cross-sectional study	Medical
(E2) Yang et al. (2018)[5]	Beijing, China	Cohort-Observational Study	Medical
(E3) Kniepeiss et al. (2003)[10]	Graz, Austria	Retrospective Study	Medical
(E4) Kniepeiss et al. (2004)[11]	Graz, Austria	Retrospective Study	Medical
(E5) Heidenhain et al. (2006)[8]	Berlin, Germany	Randomized Clinical Trial	Medical
(E6) Manzini et al. (2013)[12]	Heidelberg, Germany	Systematic Review and Meta-analysis	Medical

Source: Elaborated by the authors.

Table 2. Synthesis of primary studies according to the objective, method and main results.

Study	Objective	Method	Main Results
E1[6]	To investigate and reflect on the surgical aspects of orthotopic deceased donor liver transplantation performed in 52 transplant centers in Europe	Was used an online survey instrument with multiple-choice questions that investigated the surgical aspects of liver transplantation and addressed the piggyback portocaval shunt, graft reperfusion techniques, and other factors. Five independent senior transplant surgeons initially tested content validity.	The survey got feedback from 42 transplant centers. Of these, the most frequent reperfusion technique was portal vein reperfusion (PVFR: 64.3%, n=27/42), followed by simultaneous revascularization (SRI 17%, n=7/42), retrograde revascularization (RER 12 %, n=5/42) and arterial reperfusion first (AFR 7%, n=3/42).
E2[5]	To investigate the effects of retrograde reperfusion on the intraoperative internal environment and hemodynamics in classic orthotopic liver transplantation.	After board approval and analysis, 30 subjects were included in the study according to the inclusion and exclusion criteria. Cadaver donor data were analyzed, standardized tests were performed, and graft harvesting was standardized. All 30 patients underwent orthotopic liver transplantation with non-venous bypass. In the procedure, retrograde revascularization is performed.	All surgical procedures were successfully completed. Retrograde reperfusion employed in surgery has been shown to effectively reduce electrolyte disturbances and remove excess cytokines from the graft after recirculation in orthotopic liver transplants. Post-reperfusion syndrome in conventional liver transplants reaches 30%, while the incidence seen in this study was relatively low: 20%
E3[10]	To present a new method of reperfusion during liver transplantation.	It is a retrospective study of four years before assessing hepatocyte integrity and AST values on days 1, 3, 5 and 8 after liver transplantation. The surgical technique was unclamping the vena cava after the piggyback anastomosis.	Retrograde reperfusion efficiently removes perfusion fluid from the transplanted liver, eliminates toxic metabolites and agents, and improves the patient's earlier recovery. Of the 39 patients, only one died due to preexisting portal vein thrombosis. After the eighth day, three of the 38 survivors had an indication for retransplantation due to hepatic artery thrombosis.
E4[11]	To evaluate the influence of retrograde reperfusion in liver transplantation in Post-Hepatic Reperfusion Syndrome (PHRS).	Fifty-six consecutive liver transplants were performed using the piggyback technique with retrograde reperfusion via the vena cava. The incidence of post-reperfusion syndrome was assessed by intraoperative monitoring of mean arterial pressure through a pulmonary artery catheter.	Fifty-three patients (94.34%) were alive on day eight after liver transplantation. Only two patients who underwent liver transplantation using the retrograde reperfusion technique had SPRH (3.6%) and a drop in blood pressure greater than 30%.
E5[8]	To investigate the influence of retrograde reperfusion in liver transplantation in reducing the initial risk of graft ischemia in contrast to the increased risk of ischemic biliary lesions	132 patients undergoing orthotopic liver transplantation were included in the study and randomized into two groups. Group A underwent standard reperfusion: simultaneous arterial and portal anterograde. Group B underwent retrograde reperfusion via the vena cava before sequential anterograde reperfusion of the portal vein and hepatic artery.	In the first week after the surgical procedure, the levels of transaminases and bilirubin in group B were significantly reduced. The incidence of ischemic-type biliary injury was 12.3% in group B versus 4.55% in group A, demonstrating that retrograde reperfusion seemed beneficial to hepatocytes but harmful to the biliary epithelium.
E6[12]	To clarify which liver graft reperfusion technique leads to the best result after transplantation.	An online survey was sent to 37 transplant centers, asking which reperfusion technique would be used and whether the procedure was standardized. Systematic literature search, study selection, data extraction and meta-analysis.	Thirty transplant centers responded to the online questionnaire, and 28 were included in the study, showing that only three centers (11%) performed retrograde revascularization in transplants.

Source: Elaborated by the authors.

DISCUSSION

About 75% to 80% of the blood that arrives to irrigate the liver comes from the portal vein, which is why the technique of anterograde reperfusion with vena cava anastomosis followed by portal vein anastomosis is the most widely used since, due to the high blood flow, reperfusion is faster and more homogeneous.[6,13]In this revascularization method, the sequence performed is the anastomosis of the inferior vena cava (IVC), suprahepatic and infra hepatic, and of the portal vein (PV). After performing the anastomoses, the next step is revascularizing the hepatic parenchyma, releasing the vena cava, followed by the PV. To complete liver revascularization,

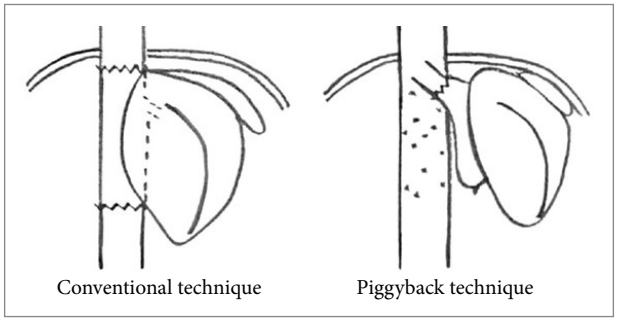
hepatic artery anastomosis is performed.[5] However, in this type of liver graft revascularization, in the conventional technique, a large amount of blood is stagnant due to the clamping of the infra diaphragmatic IVC, generating hemodynamic consequences and leading to more significant accumulation of metabolites and free radicals, given the longer warm ischemia time. Something that is minimized if the piggyback technique is used.[7]

The technique used during the procedure directly implies the hemodynamic repercussions and the time of ischemia of the organ, factors that can influence future complications, whether intraoperative or postoperative.

The conventional technique (Fig. 5) for orthotopic liver transplantation consists of retrohepatic resection of the suprahepatic and infra hepatic IVC and PV clamping during recipient hepatectomy.[1,7]

As a result, there is an interruption in the flow of the portal and inferior vena cava during the anhepatic phase. Thus, there is a decrease in venous return, cardiac output, blood pressure and perfusion of several vital organs.[7] Because of this sudden reduction in venous return, the patient may experience hemodynamic imbalance, which may be more severe in some patients.

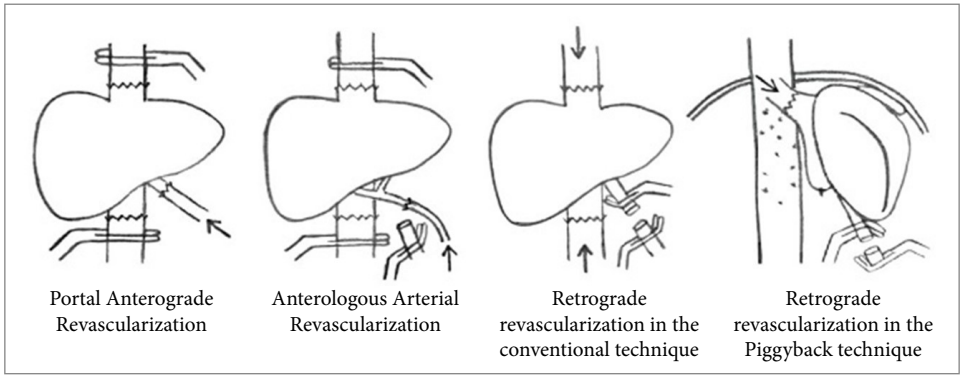
The piggyback technique (Fig 5) consists of preserving the IVC of the patient who will receive the graft. As IVC clamping is partial, there is no total occlusion of vena cava flow. Thus, the benefits of this technique are lower hemodynamic repercussions, i.e., no retrocaval dissection, reduction of the anhepatic period and greater ease in case of need for retransplantation.[7]



Source: Elaborated by the authors.

Figure 5. Techniques for graft implantation in liver transplantation.

In addition to choosing the technique used to implant the graft in the recipient patient, there is also the choice of the type of revascularization to be used. The Portal Anterograde technique is the most widely used technique for revascularizing the hepatic graft. The portal vein is first unclamped for subsequent release of the hepatic artery anastomosis, completing the total graft revascularization. In addition to this technique, another type of anterograde revascularization is arterial, which consists of releasing the hepatic artery anastomosis before releasing the portal vein anastomosis (Fig. 6).



Source: Elaborated by the authors.

Figure 6. Types of revascularization.

In this context, retrograde reperfusion was described to reduce hemodynamic implications during transplantation and ischemic graft damage in conventional and piggyback techniques[10]. The method consists of retrograde reperfusion of the vena cava and subsequent anterograde reperfusion of the portal vein. The use of this technique in orthotopic liver transplantation raised the hypothesis that perfusion under low pressure and with venous blood, little oxygenated, decreases the production of toxic metabolites and free radicals, in addition to maintaining hemodynamic stability and reducing the incidence of Post-Hepatic Reperfusion Syndrome (PHRS), when compared to the antegrade revascularization technique, which is more widely used.[5,8,10,11].

CONCLUSION

Retrograde reperfusion is more efficient in eliminating free radicals and toxic metabolites from the liver graft than anterograde revascularization. To some extent, it balances the patient hemodynamically and reduces electrolyte disturbances. In addition, decreased values of liver enzymes in the postoperative period and lower incidence of liver loss due to primary dysfunction and post-reperfusion syndrome were demonstrated. However, these indications of improvement are present in the articles included in this review, and it is not possible to reliably conclude the use of the retrograde reperfusion technique as the best revascularization technique in liver Tx, given the small amount of data available in the literature. Thus, it is understood as necessary to produce more studies that elucidate the influence of retrograde reperfusion in the reduction of warm ischemia time and, consequently, reducing the cell damage risk to the graft.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Fonseca Neto OCL; **Conception and design:** Paiva LN, Fonseca Neto OCL;**Data analysis and interpretation:** Paiva LN; **Writing:** Paiva LN**; Critical review:** Fonseca Neto OCL**; Final approval:** Fonseca Neto OCL.

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICT OF INTERESTS

Nothing to declare.

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