

ORIGINAL ARTICLE

# Hypothermic oxygenated perfusion in extended criteria donor liver transplantation—A randomized clinical trial

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## Abstract

Hypothermic Oxygenated Perfusion (HOPE) of the liver can reduce the incidence of early allograft dysfunction (EAD) and failure in extended criteria donors (ECD) grafts, although data from prospective studies are very limited. In this monocentric, open-label study, from December 2018 to January 2021, 110 patients undergoing transplantation of an ECD liver graft were randomized to receive a liver after HOPE or after static cold storage (SCS) alone. The primary endpoint was the incidence of EAD. The secondary endpoints included graft and patient survival, the EASE risk score, and the rate of graft or other graft-related complications. Patients in the HOPE group had a significantly lower rate of EAD (13% vs. 35%,  $p = .007$ ) and were more frequently allocated to the intermediate or higher risk group according to the EASE score (2% vs. 11%,  $p = .05$ ). The survival analysis confirmed that patients in the HOPE group were associated with higher graft survival one year after LT ( $p = .03$ , log-rank test). In addition, patients in the SCS group had a higher re-admission and overall complication rate at six months, in particular cardio-vascular adverse events ( $p = .04$  and  $p = .03$ , respectively). HOPE of ECD grafts compared to the traditional SCS preservation method is associated with lower dysfunction rates and better graft survival.

## KEY WORDS

ECD, HOPE, LT, SCS

## 1 | INTRODUCTION

Liver transplantation (LT) is the treatment of choice in patients with end-stage liver disease, but it is challenged by a shortage of available organs.

The use of Extended Criteria Donor (ECD) grafts has been proposed and applied to deal with the shortage of available organs. However, ECD grafts are more vulnerable to the intracellular harmful effects of ischemia, including the depletion of adenosine triphosphate (ATP) reserves, production of reactive oxygen species, and

**Abbreviations:** DCD, donors after circulatory death; EAD, early allograft dysfunction; EASE, Early Allograft Failure Simplified Estimation; ECD, Extended Criteria Donors; HOPE, Hypothermic Oxygenated Perfusion; LT, liver transplantation; SCS, static cold storage.

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alteration of cell structure and functions.<sup>1</sup> All these events can lead to severe morphological and functional damage that facilitates the onset of graft dysfunction.

Organ preservation becomes thus crucial when ECD grafts are utilized. To date, static cold storage (SCS) is the most widely used method for organ preservation due to its simplicity and effectiveness in reducing the metabolism rate and oxygen requirement.<sup>2</sup> However, SCS for ECD grafts has been associated with higher rates of early allograft dysfunction (EAD) and reduced long-term graft survival.<sup>3</sup>

Over the last decade, researchers have focused their attention on investigating new alternative strategies for organ preservation. Preclinical and clinical studies have explored the role of normothermic (35–37°C), sub-normothermic (20–25°C), and hypothermic (4–10°C) with or without oxygen machine perfusion.<sup>4</sup> Hypothermic Oxygenated Perfusion (HOPE) has been associated with better short- and long-term outcomes in LT recipients.<sup>5–7</sup>

We conducted an open-label randomized monocentric study to compare the role of HOPE and SCS in the transplantation of ECD liver grafts with the incidence of early graft dysfunction as the primary point. This is the first study that explored the role of a simple HOPE device in extended criteria brain death donors.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial design and oversight

This study was designed as an open-label, monocentric, and randomized clinical trial. Patients were stratified based on the contemporary presence of ECD liver criteria (at least five vs. more than five criteria) and randomized in a 1:1 ratio to receive a liver preserved with either HOPE after SCS during transportation (HOPE group) or with SCS alone (SCS group). Randomization was done through Medidata Balance, and it was performed when the donor was accepted for transplantation (no graft was rejected during the perfusion and the liver transplant surgical procedure started independently by the perfusion setting).

The trial protocol was approved by the Local Ethics Committee and has been previously published.<sup>8</sup> The authors were responsible for the implementation of the trial and the collection and analysis of the data. All the authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

### 2.2 | Donor and patient selection

Patients 18 years or older undergoing liver-only transplantation with ECD grafts were enrolled in the study after providing written informed consent. Donors were considered eligible for the trial if they met the United Network for Organ Sharing (UNOS) criteria for ECD.<sup>9</sup>

Exclusion criteria included donor age <18 years, split-liver recipients, LT for acute liver failure, and the development of intraoperative

surgical complications before the organ implantation. Donors after circulatory death (DCD) were also excluded due to the Italian law a “no-touch period” of at least 20 min before death declaration, causing prolonged warmed ischemia and subsequent mandatory perfusion of the organ.

### 2.3 | Hypothermic oxygenated machine perfusion

Organ perfusion was conducted with the Vitasmart (Bridge to Life, DG, USA) machine, expressly designed for ex vivo perfusion of abdominal organs. Gas analysis of the effluent perfusate was performed at the start of the perfusion (T0) and then every 30 min to determine carbon dioxide partial pressure ( $pCO_2$ ), oxygen partial pressure ( $paO_2$ ), pH, glucose, and lactate levels.

Graft perfusion and HOPE were performed in the operating room, from the start of the back-table preparation to organ implantation. HOPE started by flushing the organ at low flow values (30 ml/min) with new oxygenated perfusion fluid during the back-table preparation with the aim of removing waste products, residual microthrombi, and with the aim to give oxygen. Successively, the organ was treated with continuous HOPE until the graft was transplanted. The protocol algorithm for treatment in the HOPE group is shown in Appendix S1.

### 2.4 | Endpoint measures

The primary endpoint measure was the incidence of early allograft dysfunction (EAD). EAD was defined by the presence of at least one of the following criteria: serum bilirubin >10 mg/dl on postoperative day (POD) 7, international normalized ratio (INR) >1.6 on POD7, AST or ALT >2.000 UI/ml within the first seven postoperative days.<sup>10</sup>

Secondary endpoints measures included the Early Allograft Failure Simplified Estimation (EASE) score; the incidence of graft primary non-function (PNF) defined as patient death or the need of re-transplantation within the first seven postoperative days excluding acute vascular complications<sup>11</sup>; the incidence and severity of post-reperfusion syndrome defined as a decrease of more than 30% of in the mean arterial blood pressure or the need for aminic support to maintain hemodynamic stability; length of hospital stay; biliary and vascular complication within six months from transplant; graft survival defined as the time from transplantation to re-transplantation or patient death due to liver failure and patient overall survival.

The EASE score is calculated based on the AST, serum bilirubin, platelet count, and INR values in the first seven postoperative days, as previously described by Avolio et al.<sup>12</sup> The decision to use the EASE score rather than the L-GrAFT<sup>13</sup> score as described in the original protocol was made due to the emergence of the new EASE score as a simpler and more accurate method to predict early allograft failure and due to the lack of clarity in the correct calculation of the L-GrAFT score.<sup>14</sup>

## 2.5 | Statistical analysis

The sample size was calculated using the primary endpoint of early graft dysfunction (30% vs. 10%). The estimated number of patients was 118 ( $\alpha = .05$ , two-sided test, power of 80%). All endpoint measures were prespecified in the original protocol. Chi-square and Fisher's exact tests were used to compare categorical variables, while parametric (ANOVA) or non-parametric (Kruskal-Wallis) tests were used for continuous variables. Univariate analysis was performed to confirm the primary and secondary outcomes. Multivariate analysis using the forward stepwise logistic regression analysis was performed to identify risk factors associated with early graft dysfunction. Graft survival outcomes were evaluated with the use of the Kaplan-Meier method with a log-rank test.  $p$ -values  $<.05$  were considered statistically significant.

## 3 | RESULTS

### 3.1 | Patients

From December 2018 to January 2021, 135 potential ECD grafts were randomized, of which 110 were utilized for LT (Figure 1). Twenty-five grafts were excluded because of an unacceptable donor risk ( $n = 4$ ) or non-eligibility after macroscopic ( $n = 10$ ) or microscopic ( $n = 11$ ) evaluation. The baseline characteristics of recipients and donors included in the study are shown in Table 1. The two trial groups were comparable in terms of baseline clinical and demographic characteristics.

### 3.2 | Primary endpoint

Early allograft dysfunction occurred in seven of the 55 patients (13%) in the HOPE group and in 19 of the 55 patients (35%) in the SCS group ( $p = .007$ , risk difference [RD] 0.218, 95% confidence interval [CI] 0.065–0.372). Post hoc power analysis was performed which showed the study to be slightly underpowered (110 patients

enrolled vs. A total of 118 required to achieve 80% power). The modified number needed to treat (NNT) to prevent one additional event was 4.6.

### 3.3 | Secondary endpoints

Analysis of the primary and secondary endpoint measures are shown in Table 2. The median EASE score was -3.300 and -3.500 in the HOPE and SCS groups respectively ( $p = .64$ ). Grafts were then categorized based on the risk score, where those classified at intermediate or higher risk for graft failure at 90 days were less frequent in the HOPE group (one vs. six cases,  $p = .05$ , RD 0.091, 95% CI 0.001–0.181).

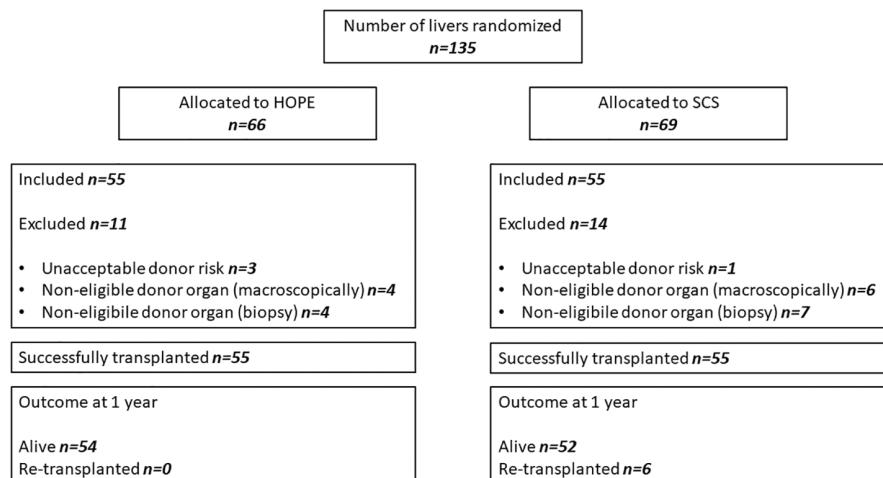
The rate of re-transplantation was significantly lower in the HOPE group (0% vs. 11%,  $p = .03$ , NNT of nine). The length of hospital stay was similar between the two groups (median of 18 and 17 days, respectively,  $p = .66$ ), however, patients in the HOPE group were associated with a lower rate of re-admission at six months (20% vs. 38%,  $p = .04$ ).

The incidence of either biliary or vascular complications at six months was similar between the two groups. Patients in the HOPE group were associated with lower rates of acute and/or chronic rejection (four vs. nine cases,  $p = .24$ ) and cardiovascular complications (three vs. 11 cases,  $p = .04$ ). A detailed breakdown of posttransplantation adverse events at six months is shown in Table 3.

The median follow-up period was 473 days (interquartile range [IQR] 236–618). The rate of graft failure at one year was higher in the SCS group (2% vs. 13%,  $p = .03$ , RD 0.109 95% CI 0.014–0.204). The log-rank test confirmed that patients in the HOPE group had higher graft survival at one year ( $p = .03$ ). We did not find significant differences between the two groups in the overall survival analysis ( $p = .52$ , log-rank test).

### 3.4 | Variables indicative of organ quality

We investigated factors associated with the development of EAD. Machine perfusion with HOPE, macrosteatosis of the graft, and



**FIGURE 1** Flowchart of eligible and included patients in the study

**TABLE 1** Recipient and donor baseline characteristics

|                                    | HOPE group<br>(n = 55) | SCS group<br>(n = 55) |
|------------------------------------|------------------------|-----------------------|
| Recipients                         |                        |                       |
| Age                                |                        |                       |
| Median                             | 57                     | 60                    |
| IQR                                | 47–65                  | 53–66                 |
| Male sex-no. (%)                   | 41 (74%)               | 39 (71%)              |
| BMI                                |                        |                       |
| Median                             | 25.4                   | 25.3                  |
| IQR                                | 22.9–28.7              | 22.5–28.4             |
| Etiology                           |                        |                       |
| Cholestatic disease                | 7                      | 2                     |
| Viral                              | 7                      | 10                    |
| Alcoholic                          | 2                      | 5                     |
| Metabolic                          | 3                      | 0                     |
| Autoimmune                         | 2                      | 1                     |
| Tumors                             | 30                     | 35                    |
| HCC and cirrhosis                  | 2                      | 0                     |
| Other                              | 2                      | 2                     |
| Other                              |                        |                       |
| MELD score                         |                        |                       |
| Median                             | 15                     | 14                    |
| IQR                                | 10–18                  | 9–20                  |
| Previous abdominal surgery—no. (%) | 38 (69%)               | 31 (56%)              |
| Portal vein thrombosis—no (%)      | 13 (24%)               | 12 (22%)              |
| Presence of HCC                    | 30 (55%)               | 35 (64%)              |
| Preservation time (min)            |                        |                       |
| Median                             | 400                    | 420                   |
| IQR                                | 360–480                | 360–450               |
| SCS-median (IQR)                   | 255 (215–325)          | 420 (360–450)         |
| HOPE-median (IQR)                  | 145 (120–185)          | -                     |
| Donors                             |                        |                       |
| Age                                |                        |                       |
| Median                             | 76                     | 72                    |
| IQR                                | 64–81                  | 59–77                 |
| Male sex-no. (%)                   | 31 (56%)               | 33 (6%)               |
| BMI                                |                        |                       |
| Median                             | 26.0                   | 26.0                  |
| IQR                                | 23.7–29.3              | 24.0–27.8             |
| Macrosteatosis (%)—median (IQR)    | 2 (0–10)               | 2 (0–10)              |
| Microsteatosis (%)—median (IQR)    | 5 (0–10)               | 5 (0–10)              |
| Fibrosis (Metavir)—median (IQR)    | 1 (1–1)                | 1 (1–1)               |
| ISHAK grade—median (IQR)           | 2 (1–2)                | 1 (1–2)               |

**TABLE 1** (Continued)

| Preservation time (min) | SCS + HOPE  | SCS alone   |
|-------------------------|-------------|-------------|
| Donor Risk Index (DRI)  |             |             |
| Median                  | 1.846       | 1.766       |
| IQR                     | 1.719–1.908 | 1.545–1.908 |

operation time resulted in significant predictive factors in the univariate analysis, of which only the first and the latter remained significantly associated with the development of EAD in the stepwise multivariate regression model ( $p = .005$ , RD 0.234, 95% CI 0.087–0.382 and  $p = .009$ , RD -0.001, 95% CI -0.0001 to 0.001). The details of the univariate and multivariate analysis are shown in Appendix S3.

In addition, we explored the role of perfusate parameters including pH, paO<sub>2</sub>, pCO<sub>2</sub>, glucose, and lactate levels at the beginning (T0) and at the end (T1) of the flushing and perfusion of the graft in predicting the development of EAD in the HOPE group. Only the lactates level at the end of flushing resulted in an independent predictor of EAD in the multivariate analysis ( $p = .01$ , RD -0.011, 95% CI -0.285 to 0.007). Details of the univariate and multivariate analysis are shown in Appendix S4.

## 4 | DISCUSSION

This study is the first randomized trial involving ECD for LT showing an improved graft outcome due to the oxygenated perfusion after a period of SCS; another randomized study found a lower rate of complications and EAD but not different graft survival<sup>15</sup> and another recent paper found a better graft and patient survival but it was a retrospective study.<sup>16</sup>

The trial met its primary endpoint demonstrating a reduction of the EAD in the study group and consequently an improved graft survival, which has never been reported in other randomized studies.

One previous randomized study showed a reduction of the peak transaminases and EAD using normothermic oxygenated perfusion, but the graft survival did not differ among groups.<sup>17</sup> Another recent randomized trial showed a reduction of biliary complications using end-hypothermic oxygenated perfusion in DCD, but still, the graft survival did not reach any statistical significance.<sup>7</sup>

Our trial introduces a very simple oxygenated machine perfusion system through only the portal vein<sup>6,18</sup> (the artery was not perfused) applied after a period of conventional SCS, characterized by a period of graft flushing during the back-table preparation first and then conventional recirculation, as previously reported.<sup>8,18</sup> This strategy reduces as much as possible the cold ischemic time, which has been related to graft outcome in many previous studies.<sup>19–22</sup> Starting with HOPE at the time of back table increased the time of HOPE in combination with a short time of cold ischemic time and probably

**TABLE 2** Primary and secondary endpoints

|   | HOPE group (n = 55) | SCS group (n = 55)   | Adjusted risk difference<br>(95% CI) | p value |
|---|---------------------|----------------------|--------------------------------------|---------|
| EAD-no. (%)                                       | 7 (13%)             | 19 (35%)             |                                      | .007    |
| RD  |                     |                      | 0.218 (0.065–0.372)                  | .005    |
| EASE score  |                     |                      |                                      |         |
| Median  | -3.300              | -3.500               | —                                    | .635    |
| IQR   | -3.80 to -2.80      | -4.10 to -2.60       |                                      |         |
| Extremely low/low risk                            | 54 (98%)            | 49 (89%)             |                                      | .113    |
| Intermediate or higher risk                       | 1 (2%)              | 6 (11%)              |                                      |         |
| RD  |                     |                      | 0.091 (0.001–0.181)                  | .047    |
| PNF-no. (%)                                       | 0 (0%)              | 2 (4%)               | —                                    | .49     |
| Re-transplantation-no. (%)                        | 0 (0%)              | 6 (11%) <sup>a</sup> | —                                    | .027    |
| Post-reperfusion syndrome-no. (%)                 | 30 (55%)            | 26 (47%)             | —                                    | .45     |
| Length of hospital stay (days)                    |                     |                      |                                      | .66     |
| Median  | 18                  | 17                   | —                                    |         |
| IQR   | 15–28               | 11–41                |                                      |         |
| ICU stay (days)                                   |                     |                      | —                                    | .50     |
| Median  | 4                   | 4                    |                                      |         |
| IQR   | 3–8                 | 3–6                  |                                      |         |
| Hepatic biliary or vascular complications-no. (%) | 9 (16%)             | 12 (22%)             | —                                    | .47     |
| Graft failure at 1 year—no. (%)                   | 1 (2%)              | 7 (13%)              | 0.110 (0.014–0.204)                  | .058    |
| CCI ≥3b—no. (%)                                   | 12 (22%)            | 18 (33%)             | —                                    | .20     |

<sup>a</sup>Two primary non-function (PNF), four delayed graft non-function.

this combination was the cause not only of better EAD rates but also a better graft survival, as reported in our study differently from others.

The improved graft function in the study group can lead to a lower rate of post-operative complications and a significantly lower rate of re-admission of the patient after LT, as observed in our cohort. Differently from previously reported experiences,<sup>4–7,23</sup> the rate of biliary complications was not different between the two groups. This can be explained by the very low rate of such complications in both arms (13%) and by the fact that the study did not include DCD. For this type of donor, in Italy all liver transplant centers perform ex situ perfusion<sup>19,24</sup> to overcome the prolonged warm ischemia time due to the mandatory 20 min no-touch period, for which reason we could not plan a randomized trial in this setting.

The recipients in our cohort did not have a high MELD score because matching ECD and very sick patients are usually avoided to reduce the risk of transplant failure.<sup>25</sup> Such finding was also reported in previous similar studies, where the median MELD score was 13 to 16.<sup>7,17</sup> The excellent outcome in the study group may induce to explore the use of ECD grafts even in high MELD recipients following our protocol, but not in a randomized fashion.

The strategy of flushing the graft during the back-table to remove cytokines has been previously reported by our group in a series of 10 livers and 11 kidneys,<sup>18</sup> while other recently published pre-clinical

and clinical studies have shown the protective effect of the perfusate and cytokines absorption during kidney and lung perfusion.<sup>26,27</sup> Differently to these studies, we do not use any absorber, instead, we flush the graft for 30–60 min. The perfusate fluid analysis was associated with the rate of EAD and future molecular analysis will help to evaluate the graft function during the hypothermic perfusion, as suggested by other studies.<sup>28</sup>

The present trial showed an improved graft survival and therefore the cost of the study procedure may be justified by the better outcome. Furthermore, the reduction for re-transplantation and re-admission rates<sup>29,30</sup> may confirm the cost-analysis benefit.

The study procedure is simple and easy, as demonstrated by the absence of any adverse events; other ex vivo perfusion system presented some risk of graft failure related to the procedure.<sup>31</sup>

One concern of this study may be the quality of the donors. Some authors could sustain a good outcome that could be reached even without any perfusion system. However, the median DRI<sup>3</sup> in our cohort was higher than in other similar randomized studies<sup>7,17</sup> and the reported better outcome can justify even a higher number of patients to treat to obtain the benefit.

This last concept may be the reason why end-hypothermic oxygenated perfusion was not found to be related to improved graft function and survival in two recent randomized trials for kidney transplantation.<sup>32,33</sup> An important issue coming from these studies was the reduction of the acute rejection in the HOPE group, which

**TABLE 3** Detailed breakdown of adverse event complications at six months after LT

|                               | HOPE group<br>(n = 55) | SCS group<br>(n = 55) | p value |
|-------------------------------|------------------------|-----------------------|---------|
| Hepatic                       |                        |                       |         |
| Biliary leak                  | 2 (4%)                 | 1 (2%)                | n.s.    |
| Biliary stricture             | 2 (4%)                 | 2 (4%)                | n.s.    |
| Biliary other                 | 3 (5%)                 | 4 (7%)                | n.s.    |
| HA aneurism                   | 1 (2%)                 | 0 (0%)                | n.s.    |
| HA thrombosis                 | 1 (2%)                 | 0 (0%)                | n.s.    |
| HV thrombosis                 | 0 (0%)                 | 2 (4%)                | n.s.    |
| HV stenosis                   | 0 (0%)                 | 2 (4%)                | n.s.    |
| PV thrombosis                 | 0 (0%)                 | 1 (2%)                | n.s.    |
| Dysfunction                   | 9 (16%)                | 21 (38%)              | .010    |
| Rejection                     | 4 (7%)                 | 9 (16%)               | n.s.    |
| Infections                    |                        |                       |         |
| Blood                         | 16 (29%)               | 10 (18%)              |         |
| Chest                         | 5 (9%)                 | 10 (18%)              |         |
| Biliary                       | 1 (2%)                 | 5 (9%)                |         |
| Abdominal                     | 4 (7%)                 | 1 (2%)                |         |
| Urinary tract                 | 2 (4%)                 | 1 (2%)                |         |
| Wound                         | 2 (4%)                 | 2 (4%)                |         |
| Other                         | 6 (10%)                | 6 (10%)               |         |
| Cardio-vascular               |                        |                       |         |
| Arrhythmia                    | 1 (2%)                 | 6 (10%)               |         |
| Pulmonary embolism            | 0 (0%)                 | 3 (5%)                |         |
| Deep vein thrombosis          | 2 (4%)                 | 1 (2%)                |         |
| Other                         | 0 (0%)                 | 1 (2%)                |         |
| Gastro-intestinal—no.         | 4 (7%)                 | 4 (7%)                | n.s.    |
| Genito-urinary                | 16 (29%)               | 23 (42%)              | n.s.    |
| Renal insufficiency           | 15 (27%)               | 20 (37%)              |         |
| Other                         | 1 (2%)                 | 3 (5%)                |         |
| Respiratory—no.               | 2 (4%)                 | 5 (9%)                | n.s.    |
| Fluid collection              | 20 (36%)               | 22 (40%)              | n.s.    |
| Abdominal                     | 11 (20%)               | 11 (20%)              |         |
| Pleural                       | 9 (16%)                | 11 (20%)              |         |
| Bleeding                      | 13 (24%)               | 10 (18%)              | n.s.    |
| Transfusion without bleeding  | 11 (20%)               | 7 (13%)               |         |
| Bleeding                      | 2 (4%)                 | 3 (5%)                |         |
| Other complications           | 10 (18%)               | 8 (13%)               | n.s.    |
| Re-intervention               | 6 (10%)                | 9 (16%)               | n.s.    |
| Biliary complications         | 5 (9%)                 | 2 (3%)                |         |
| Re-transplantation            | 0.0 (0%)               | 6 (11%)               |         |
| Other surgical emergency      | 1 (1%)                 | 1 (1%)                |         |
| Re-admission                  | 11 (20%)               | 21 (38%)              | .036    |
| Biliary associated procedures | 4 (7%)                 | 6 (12%)               |         |

**TABLE 3 (Continued)**

|                      | HOPE group<br>(n = 55) | SCS group<br>(n = 55) | p value |
|----------------------|------------------------|-----------------------|---------|
| Infection            | 2 (4%)                 | 1 (1%)                |         |
| Surgical emergency   | 2 (4%)                 | 3 (5%)                |         |
| Other medical causes | 3 (5%)                 | 11 (20%)              |         |

was also observed in our cohort (7% vs. 14%), although it did not reach any statistical significance. We did not perform a protocol biopsy in the post-operative period, but such type of monitoring, even at the risk of bleeding, needs to be included in a future study on the liver and HOPE to evaluate the post-operative changes in the immunological fields and further studies in the animal model need to investigate this aspect.

Another interesting aspect is the potential protective effect of HOPE for tumor recurrence in the case of recipients with HCC, as recently reported.<sup>34</sup> In our series we had one tumor recurrence among 30 cases with HCC in the study group and four among 35 in the control group, but a minimum follow-up of two years and a higher sample size are required for any analysis.

## 5 | CONCLUSIONS

In conclusion, we reported a single-center randomized study of oxygenated end-hypothermic perfusion using a simple device with flushing and recycling able to obtain an improved graft function and survival, using extended criteria brain death donors.

## AUTHOR CONTRIBUTIONS

The study design was conceived by MR. Trial management and oversight were done by MR, GG, VF, AS, MCM, MS, MDG, CZ, FO, and MC. Patient recruitment and data collection were done by all authors. Statistical analysis was done by MS and GD. GG, VRB, LM, and AL did the literature search and initial manuscript preparation, and all authors reviewed and approved the final manuscript.

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## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

## DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author (MR) on request according to national and international legislation regarding privacy and data protection.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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