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Original Article

A French multicenter randomized controlled trial of hypothermic oxygenated perfusion in extended criteria donor liver transplantation

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Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CCI, comprehensive complication index; CI, confidence interval; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; EASE, early allograft failure simplified estimation; ECD, extended criteria donor; GGT, gamma-glutamyltransferase; HOPE, end-ischemic hypothermic oxygenated perfusion; ICU, intensive care unit; IRI, ischemia/reperfusion injury; L-GRAFT, liver graft assessment following transplantation; LT, liver transplantation; MEAF, model for early allograft function; MELD, model for end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; NMP, normothermic machine perfusion; PNF, primary nonfunction; POD, postoperative day; RCT, randomized controlled trial; SCS, static cold storage.

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ABSTRACT

The aim of this study was to assess the efficacy of end-ischemic hypothermic oxygenated perfusion (HOPE) used before liver transplantation (LT) with extended criteria donor (ECD) organs from donation after brain death (DBD) in reducing early allograft dysfunction (EAD) compared with static cold storage (SCS). Between 2019 and 2023, 262 ECD-DBD grafts from 8 French centers were randomly assigned for LT either after SCS (control group, n = 131) or after SCS and subsequent 1-4 h single portal HOPE before implantation (HOPE group, n = 131). The primary endpoint was the incidence of EAD. HOPE resulted in a significantly lower rate of EAD (17.6% vs 30.5%, $P = .01$). Severe complication rate (61.5% vs 52.4%, $P = .15$), comprehensive complication index (49 [34-65] vs 46 [35-65], $P = .78$), and 90-day mortality (5.3% vs 2.3%, $P = .20$) did not differ significantly between the control and HOPE groups, respectively. Four patients (4.9%) in the control group and 3 patients (3.3%) in the HOPE group experienced ischemic cholangiopathy at 1 year after LT ($P = .71$). In older patients receiving grafts with more than 6 hours of cold ischemia, HOPE was associated with a lower severe complication rate (26% vs72%, $P = .005$). HOPE in ECD grafts from DBD for LT reduces EAD with little clinical impact on morbidity and survival in recipients with low model for end-stage liver disease scores. Older recipients with long cold ischemia time might benefit the most.

Clinical trial number: NCT03929523.

1. Introduction

Given the scarce donor supply, an increasing number of so-called marginal or extended criteria donor (ECD) organs are used for liver transplantation (LT), grafts that were previously rarely considered.[1] While there is no international consensus on the definition of ECD organs, the EuroTransplant organ procurement organization reports that 40% to 50% of liver grafts are provided from ECD in Europe. These ECD liver grafts are known to be more vulnerable to ischemia/reperfusion injury (IRI), which includes adenosine triphosphate depletion, accumulation of metabolites, cellular necrosis, production of reactive oxygen species, proinflammatory response, and subsequent loss of viable cells.[2] Clinically, ECD grafts are associated with a higher rate of early allograft dysfunction (EAD), primary nonfunction (PNF), and ischemic cholangiopathy.[3] Although graft function finally recovers, EAD is associated, in turn, with increased recipient susceptibility to sepsis,[4] longer intensive care unit (ICU) and hospital stays,[5-7] graft loss,[8] greater morbidity and mortality after LT,[9,10] and potentially higher costs.[11]

Liver machine perfusion has been developed to alleviate IRI and has changed the landscape of organ preservation. Among all available protocols, the end-ischemic hypothermic oxygenated perfusion (HOPE) is technically easy to apply either by simple portal vein perfusion or dual HOPE.

Although the benefits of HOPE before LT have been clinically demonstrated in donation after cardiac death (DCD),[12,13] there are few arguments for any benefit in good-quality liver grafts from donation after brain death (DBD).[14] Moreover, only 2 randomized controlled trials (RCTs) with low sample size have tested this perfusion strategy in pure cohorts of recipients receiving ECD organs.[15,16]

Finally, the economic impact of machine perfusion, including machine costs and the potential reduction in complications, is still a matter of debate.[17] To our knowledge, no comprehensive cost analysis of LT after HOPE in an RCT has been carried out yet.

The aim of this multicenter RCT was to assess the efficacy of HOPE used before LT with ECD-DBD grafts in reducing postoperative EAD and failure compared with conventional static cold storage (SCS). A secondary objective was to measure and compare the 1-year patient care costs of LT according to the 2 strategies.

2. Materials and Methods

2.1. Trial design

The HOPExt trial is a comparative open-label multicenter national prospective randomized controlled superiority study in 2 parallel groups using SCS as control. Allocated liver grafts were

randomly assigned in a 1:1 ratio to be preserved either by conventional SCS (control group) or by cold storage plus subsequent 1 to 4 hours of HOPE (HOPE group). The study was conducted in 8 transplantation centers located in university hospitals throughout France.

Randomization was performed after the harvesting team had assessed the graft according to the center's practice. A stratification was applied according to center and MELD score at the time of transplantation using a cut-off at 30 (MELD scores <30 vs ≥ 30). Within strata, a block randomization design was used (blocks of size 2). The block size was not disclosed in the protocol, making it impossible to predict the randomization sequence. The randomization process was centralized and carried out using Ennov Clinical software. Owing to the nature of the surgical procedure, it was not possible to blind the surgical and the anesthesiologist teams to the group allocation. Because the patient could not impact the study outcomes after LT, there was no need to blind the patient. The study protocol was approved by a human research ethics committee (*Comité de Protection des Personnes Ile de France III*) on June 5, 2019, under the reference number 3688-I. The trial also received approval from the French regulatory agency (*Agence National de Sécurité du Médicament et des Produits de Santé)* on June 20, 2019 (190004B-13). Written informed consent was obtained from all participants.

2.2. Trial patients

All recipients ≥ 18 years of age who were candidates for an elective primary LT, whatever the indication, were eligible for inclusion in the trial. Liver grafts were recovered from an ECD-DBD, defined as the presence of at least 1 of the following published criteria: donor age >65 years, ICU stay >7 days, body mass index >30 kg/m^2, proven biopsy macro-steatosis $\geq 30\%$, natremia >155 mmol/L at any time, serum aspartate aminotransferase (AST) levels >150 IU/L at any time, and serum alanine aminotransferase (ALT) levels >170 IU/L at any time.[1,18] Noninclusion criteria included fulminant hepatic failure, retransplantation, split LT, living donor LT, DCD graft, and combined LT.

2.3. Intervention procedures

In the HOPE group, after conventional cold storage in Institut Georges Lopez (IGL-1) solution (Institute George Lopez, Lissieu, France) at 4 °C during transportation to the transplant center, ECD-DBD liver grafts were perfused with HOPE via the portal vein only for a minimum of 1 hour (ideally 1-4 hours) after the "back-table" phase and concomitantly to the recipient's hepatectomy. All centers used the CE-certified Liver Assist perfusion device (XVivo, Göteborg, Sweden). The targeted portal vein flow rate was 150 to 250 mL/min with a pressure of 3 mmHg and a perfusate temperature between 8 and 12 °C. The perfusate consisted of 3 L of recirculating Belzer MPS (Bridge to Life Ltd, London, United Kingdom) with active oxygenation (70 kPa).

In the control group, the gold standard SCS technique (4 °C) was used with IGL-1 (Lissieu, France) solution from graft harvesting until LT as routine practice in the 8 centers.

2.4. Endpoint measures

The primary endpoint was the rate of patients with EAD according to Olthoff et al,[7] defined by the presence of at least 1 of the following criteria: serum bilirubin level >10 mg/dL (ie, 171 μmol/L) on postoperative day (POD) 7, international normalized ratio >1.6 on POD 7, and AST or ALT level >2000 IU/L within the first 7 PODs. PNF of the graft was the very last stage of any EAD and was defined by the presence of either graft loss or the patient's death within the first 7 PODs.

The secondary endpoints were liver injury and function assessed by measurement of the area under the curve (AUC) values of AST, ALT, bilirubin, alkaline phosphatase (AP), gamma-glutamyltransferase (GGT) levels, international normalized ratio value and factor V; kidney function assessed using serum creatinine level and glomerular filtration rate; blood transfusions; occurrence of postreperfusion syndrome defined as a 50% decrease in median arterial pressure during the 5 minutes following the graft revascularization; duration of surgery; 90-day mortality and morbidity assessed by major posttransplant complications (Dindo-Clavien classification ≥ 3) and the comprehensive complication index (CCI)[19]; length of ICU and hospital stay; and recipient and graft survival at 3 months and 1 year after LT. Laboratory measurements were taken at 6 hours and 12 hours and every day until POD7 after transplantation. Model for early allograft function (MEAF) scores (0-10),[20] liver graft assessment following transplantation (L-GRAFT) scores (-6 to $+6$),[21] and early allograft failure simplified estimation (EASE) scores,[22] were calculated. Intrahepatic and extrahepatic biliary complications were assessed using serum levels of cholestasis parameters (bilirubin, GGT, and AP levels) every 3 months for 1 year and liver contrast-enhanced magnetic resonance imaging, including a magnetic resonance cholangiopancreatography (MRCP) at 12 months after LT. Postreperfusion liver biopsy was performed to assess histologic changes, including levels of IRI and necrosis. Histologic assessment was centralized and performed by an experienced pathologist in LT (V.H.).[23]

2.5. Cost analysis

The comparison of patient care costs was carried out during the clinical trial from a hospital perspective and over a time horizon of 12 months from surgery. The evaluated expenditure items included the surgical procedure (valued with a micro-costing method), the initial hospitalization for surgery, and the resources consumed during the 12-month follow-up (new hospitalizations, consultations, laboratory tests, and radiological examinations). The surgical procedure included the costs of the consumables associated with HOPE and of the staff time dedicated to the use of the machine, as well as depreciation

and maintenance costs of the machine. All costs were expressed in euros (€) at the 2023 price year and adjusted for inflation. Further details on the protocol were published elsewhere.[24]

2.6. Statistical analysis

The trial was powered to detect an expected decrease in EAD rate from 30% in the control group to 15% in the HOPE group. This 50% decrease in EAD was based on previous preliminary clinical studies.[12,25] For the sample size calculation, to achieve a power of 80%, a significance level of 0.05 was considered for a 2-sided test. This resulted in a sample size of 119 per arm, 238 in total. The sample size was then increased to 133 per arm, 266 in total, to account for a 10% proportion of dropouts.

All randomized and transplanted subjects were considered for the analysis. Descriptive summary statistics for continuous variables were the number of observations (n), median, and 25th and 75th percentiles (interquartile range). Descriptive summary statistics for categorical data were frequency counts and percentages (N%). Categorical variables were compared between the 2 study arms using the chi-square test or the Fisher exact test, as appropriate, whereas continuous variables were compared using the Student *t*-test in the case of normal distribution or the Mann-Whitney *U*-test otherwise. Normality was tested using the Shapiro-Wilk test. Graft and patient survival were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A Cox proportional hazard model was used to assess the effect of HOPE (vs control) on survival. Hazard ratios are presented together with the 95% confidence intervals (CIs).

As cost data were nonnormal and right-skewed, nonparametric bootstrapping (bias-corrected and accelerated method; R = 10 000) was used for the cost analysis.[26] Costs per group and cost differences were presented using means associated with their bias-corrected and accelerated bootstrap 95% CI. A *P* value $<.05$ was considered statistically significant.

3. Results

3.1. Patients

Between September 2019 and March 2023, 266 ECD-DBD liver grafts were randomly assigned for LT either after conventional SCS (control group, n = 133) or HOPE (HOPE group, n = 133). After randomization, 4 patients were excluded: 2 from the control group and 2 from the HOPE group. The reasons for exclusion were unexpected peritoneal carcinomatosis after recipient laparotomy (n = 1 with canceled LT) and noninclusion criteria, including grafts without extended criteria (n = 2) and a patient under legal protection (n = 1). Overall, 262 LTs were performed within the trial, with 131 patients in each study arm. All patients but 1 completed the 1-year follow-up, except for deaths during this time (n = 25). One patient was lost to follow-up at 3 months after moving abroad (Fig. 1).

Baseline characteristics of liver donors and liver graft preservation are shown in Table 1. After randomization, the 2 groups were well balanced except for more liver donors with serum

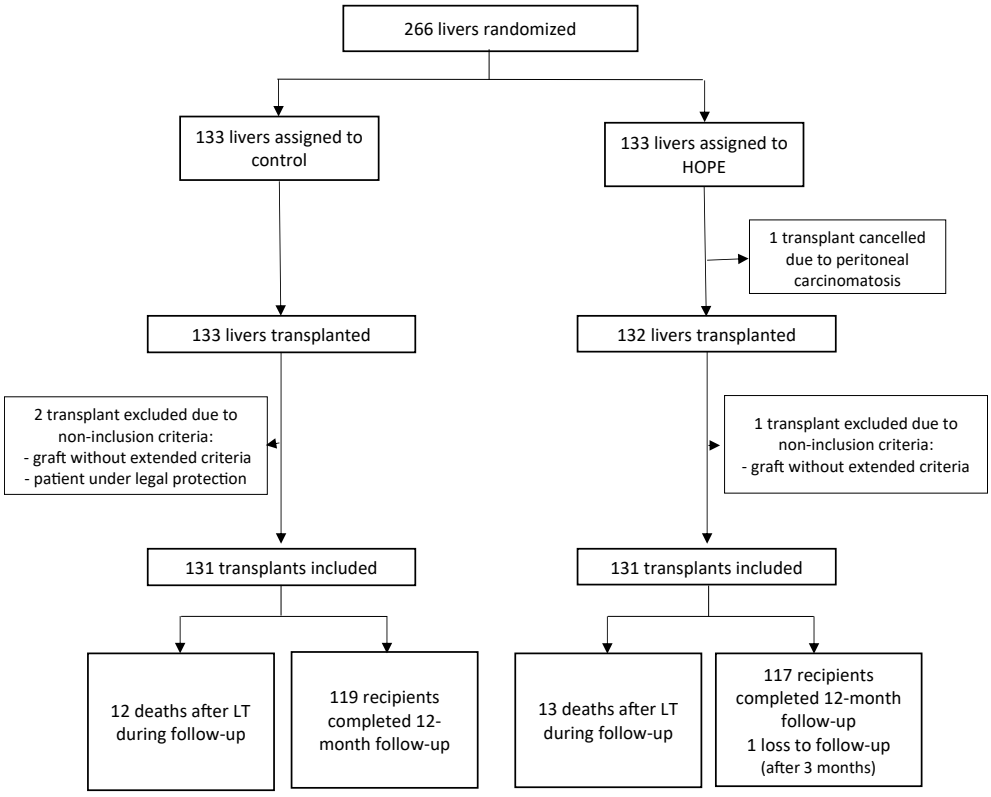

Figure 1. CONSORT diagram for donor livers enrolled in the trial. CONSORT, Consolidated Standards of Reporting Trials. HOPE, end-ischemic hypothermic oxygenated perfusion; LT, liver transplantation.

Table 1
Characteristics of liver donors and liver graft preservation.

Variables	Overall	Control	HOPE	*P*
N	262	131	131	
Donor age, y	70 [57-76]	70 [55-76]	68 [57-76]	.82
Donor sex, male %	56.9	55.0	58.8	.53
Donor BMI, kg/m^2	26.2 [23.0-30.1]	26.8 [23.1-31.1]	25.8 [22.9-29.3]	.37
Donor cause of death				.24
- Cerebral hemorrhage	153 (58.4)	77 (58.8)	76 (58)	
- Cerebral trauma	50 (19.1)	22 (16.8)	28 (21.4)	
- Anoxia	39 (14.9)	18 (13.7)	21 (16.0)	
- Other	20 (7.6)	14 (10.7)	6 (4.6)	
Preservation solution				.30
- Institut Geoges Lopez-1 (IGL-1)	219 (83.9)	113 (86.3)	106 (81.5)	
- Other	42 (16.1)	18 (13.7)	24 (18.5)	
ECD graft selection				
- Donor age >65 y	158 (60.5)	79 (60.8)	79 (60.3)	.94
- Donor ICU >7 d	24 (9.2)	13 (10.0)	11 (8.4)	.65
- Donor BMI >30 kg/m^2	64 (24.4)	36 (27.5)	28 (21.4)	.25
- Macrosteatosis ≥30%	11 (4.2)	6 (4.6)	5 (3.8)	.75
- Serum sodium level >155 mmol/L	36 (13.8)	12 (9.2)	24 (18.3)	.033
- Serum AST level >150 IU/L	63 (24.0)	32 (24.4)	31 (23.7)	.89
- Serum ALT level >170 IU/L	43 (16.4)	20 (15.3)	23 (17.6)	.62
No. of ECD criteria reached, n (%)				.91
1 of 7	162 (62.1)	82 (63.1)	80 (61.1)	
2-3 of 7	92 (35.2)	45 (34.6)	47 (35.9)	
>3 of 7	7 (2.7)	3 (2.3)	4 (3.1)	
Donor risk index	1.71 [1.41-1.89]	1.76 [1.38-1.90]	1.70 [1.43-1.89]	.60
BAR score	6 [4-9]	5 [3-9]	7 [4-9]	.42
Duration of cold storage, min	339 [285-426]	388 [313-483]	316 [263-360]	<.001
Duration of HOPE, min	-	-	112 [83-170]	
Total preservation time,[a] min	420 [343-491]	388 [313-483]	434 [380-510]	.003
Warm ischemia time, min	47 [37-57]	44 [37-54]	50 [38-59]	.65
Oxygen pressure end of perfusion, kPa	-	-	75 [38-102]	-
Liver weight, g	1402 [1183-1614]	1433 [1205-1630]	1382 [1167-1600]	.45
Graft histology (reperfusion biopsy)				
Macrosteatosis, % (n = 243)	0 [0-5]	0 [0-5]	0 [0-5]	.34
Microsteatosis, % (n = 243)	0 [0-12.5]	0 [0-10]	0 [0-20]	.22
IRI (n = 243)				.76
- No	45 (18.5)	20 (16.7)	25 (20.3)	
- light	109 (44.9)	53 (44.2)	56 (45.5)	
- moderate	72 (29.6)	39 (32.5)	33 (26.8)	
- severe	17 (7.0)	8 (6.7)	9 (7.3)	

(*continued on next page*)

Table 1 (*continued*)

Variables	Overall	Control	HOPE	*P*
Fibrosis (n = 245)				.61
- F0	139 (56.7)	73 (59.8)	66 (53.7)	
- F1	101 (41.2)	48 (39.3)	53 (43.1)	
- F2	3 (1.2)	1 (0.8)	2 (1.6)	
- F3	1 (0.4)	0 (0.0)	1 (0.8)	
- Undetermined	1 (0.4)	0 (0.0)	1 (0.8)	

Continuous variables are presented as median [interquartile range] and categorical variables as n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAR, balance of risk; BMI, body mass index; ECD, extended criteria donor; HOPE, end-ischemic hypothermic oxygenated perfusion; ICU, intensive care unit; IRI, ischemia/reperfusion injury.
[a] Total preservation time = duration of cold storage + duration of machine perfusion.

sodium levels >155 mmol/L as extended criteria in the HOPE group. About two-thirds of the liver donors had only 1 ECD criterion, whereas one-third reached 2 to 3 criteria. Donor risk index was similar between both groups (1.76 [1.38-1.90] in the control group vs 1.70 [1.43-1.89] in the HOPE group, $P = .60$). According to the study protocol, the duration of total preservation time was significantly longer in the HOPE group (434 [380-510] vs 388 [313-483] minutes, $P = .003$) with shorter cold ischemia time in the HOPE group (316 [263-360] vs 388 [313-483] minutes, $P < .001$) and a median HOPE perfusion time of 112 (83-170) minutes.

Baseline characteristics of liver transplant recipients are shown in Table 2. MELD score before LT was similarly low in both groups (14 [9-22] in the control group vs 17 [11-23] in the HOPE group, $P = .07$).

3.2. Primary endpoint

The rate of EAD was almost twice as low in the HOPE group compared with the control group (17.6%, 95% CI [11.0-24.1] vs 30.5%, 95% CI [22.7-38.4], $P = .014$), and PNF occurred in 1 vs 6 patients in the HOPE and control groups, respectively, without reaching statistical significance ($P = .12$). After the study was designed, new scores assessing EAD were developed for which the HOPExt trial was not powered: there was no difference in the median MEAF, L-GRAFT10, and EASE scores between the 2 groups (Table 3).

3.3. Secondary endpoints

Laboratory values during the first week after LT showed that the HOPE group was associated with a 24%-decrease in the peak of AST levels ($P = .009$) and a 21%-decrease in the peak of ALT levels ($P = .021$) compared with the control group (Table 3, Fig. 2). Although GGT AUC value (AUC value day 1-7) and AP AUC value (day 1-7) were significantly decreased in the HOPE group, total bilirubin, GGT, and AP serum levels were similar between both groups (Table 3).

Histologic assessment of postreperfusion liver biopsy showed similar IRI of the graft between groups (Table 1). Almost half of the grafts had light IRI, and less than 7% of them showed severe injury.

The total number of 90-day severe complications was significantly lower in the HOPE group compared to the control group (16.2% vs 20.1%, $P = .035$). However, the proportion of patients with at least 1 Clavien ≥3a complication did not differ significantly between groups (61.5% in the control group and 52.4% in the HOPE group, $P = .15$). Within 90 days 3 (2.3%) and 7 (5.3%) patients died in the HOPE and control groups, respectively, but the difference did not reach statistical significance ($P = .20$). The overall 90-day CCI of all complications was not significantly different between the study groups (49.5 [34.3-65.1] in the control group vs 46.1 [35.4-65.3] in the HOPE group, $P = .78$). ICU and hospital lengths of stay were also similar between groups (Table 3).

The 1-year overall graft survival was 87.8% (115/131) in the HOPE group with 5 liver-related graft losses and 11 recipient-related graft losses, and 87% (114/131) in the control group with 9 liver-related graft losses and 8 recipient-related graft losses ($P = .85$) (Table 3 and Fig. 3). The 1-year patient survival was similar in both groups (90.1% vs 90.8% in the HOPE and control groups, respectively, $P = .83$) (Fig. 3).

At 1 year, an MRCP was performed in 172 recipients (66%). An ischemic (nonanastomotic stenosis) cholangiopathy was diagnosed in 3 (3.3%) patients of the HOPE group and 4 (4.9%) patients of the control group ($P = .71$) (Table 3).

3.4. Post hoc analysis

In patients aged ≥60 years, the rate of EAD was significantly lower in the HOPE group (13% vs 30% in the control group, $P = .019$), as was the proportion of 90-day severe complications (45% vs 63%, $P = .045$). In patients aged ≥60 years and with cold ischemia time >6 hours, this proportion reached 72% in the control group compared with 26% in the HOPE group ($P = .005$).

3.5. Cost analysis

The total health care cost per patient was €77 987.54 [72 948.57-83 427.96] in the HOPE group and €72 748.5 [67 000.63-

Table 2
Characteristics of liver transplant recipients.

Variables	Overall	Control	HOPE	*P*
N	262	131	131	
Recipient age, y	60 [54-65]	60 [54-65]	60 [53-65]	.88
Recipient sex, male %	80.5	80.2	80.9	.88
Recipient BMI, kg/m^2	26.8 [23.3-31.0]	27.4 [23.6-31.7]	26.3 [23.0-30.4]	.13
Underlying liver disease				
- HBV	20 (7.6)	7 (5.3)	13 (9.9)	.16
- HCV	31 (11.8)	13 (9.9)	18 (13.7)	.34
- Alcohol	172 (65.6)	86 (65.6)	86 (65.6)	1
- NASH	55 (21.0)	27 (20.6)	28 (21.4)	.88
- Autoimmune hepatitis	3 (1.1)	1 (0.8)	2 (1.5)	1
- Other	2 (0.8)	2 (1.5)	0 (0.0)	.50
HCC, n (%)	114 (43.7)	62 (47.3)	52 (40.0)	.23
Treatment before liver transplant				.75
- None	165 (63.0)	77 (58.8)	88 (67.2)	
- TACE	41 (15.6)	24 (18.3)	17 (13.0)	
- Liver surgery	5 (1.9)	2 (1.5)	3 (2.3)	
- TIPS	17 (6.5)	9 (6.9)	8 (6.1)	
- RFA	18 (6.9)	10 (7.6)	8 (6.1)	
- Other	16 (6.1)	9 (6.9)	7 (5.3)	
Cirrhotic patients, n (%)				.36
- Child A	64 (28.2)	36 (31.6)	28 (24.8)	
- Child B	80 (35.2)	41 (36.0)	39 (34.5)	
- Child C	83 (36.6)	37 (32.5)	46 (40.7)	
Laboratory MELD score before liver transplantation	16 [10-22]	14 [9-22]	17 [11-23]	.07
Transplant center				1
- Beaujon, Clichy	12 (4.6)	7 (5.3)	5 (3.8)	
- Grenoble	20(7.6)	10 (7.6)	10 (7.6)	
- La Pitié-Salpêtrière, Paris	21 (8.0)	10 (7.6)	11 (8.4)	
- Lille	41 (15.6)	21 (16.0)	20 (15.3)	
- Lyon	42 (16.0)	21 (16.0)	21 (16.0)	
- Paul Brousse, Villejuif	69 (26.3)	35 (26.7)	34 (26.0)	
- Rennes	46 (17.6)	22 (16.8)	24 (18.3)	
- Strasbourg	11 (4.2)	5 (3.8)	6 (4.6)	
eGFR mL/min				
- MDRD	91.6 [67.2-120]	94.0 [70.2-122]	89.5 [65.9-112]	.18
- CKD-EPI	92.0 [67.0-102]	93.3 [71.1-102]	90.2 [63.2-101]	.23

Continuous variables are presented as median [interquartile range] and categorical variables as n (%).
BMI, body mass index; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimate glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOPE, end-ischemic hypothermic oxygenated perfusion; MELD, model for end-stage liver disease; MDRD, Modification of diet in renal disease; NASH, nonalcoholic steatohepatitis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TIPS, transjugular intrahepatic portosystemic shunt.

Table 3
Outcome parameters.

Variables	Overall	Control	HOPE	*P*
N	262	131	131	
Intraoperative findings				
Duration of LT	374 [321-445]	367 [316-432]	382 [322-451]	.36
Intraoperative transfusion, n (%)	177 (67.6)	84 (64.1)	93 (71.0)	.23
RBC transfusion	164 (62.6)	79 (60.3)	85 (64.9)	.44
Intraoperative RBC, U	3.5 [2-6]	4 [2-6]	3 [2-6]	.65
Intraoperative fresh frozen transfusion	95 (36.3)	46 (35.1)	49 (37.4)	.70
Intraoperative fresh frozen Plasma, U	4 [3-7]	4 [3-7]	4 [3-7]	.65
Platelet transfusion	72 (27.5)	32 (24.4)	40 (30.5)	.27
Intraoperative platelet units, U	1 [1-2]	1 [1-2]	1 [1-2]	.97
Occurrence of postreperfusion syndrome	90 (34.4)	46 (35.1)	44 (33.6)	.79
Laboratory parameters				
Peak AST level, U/L	846 [547-1687]	1027 [573-2137]	777 [528-1462]	.009
AST level AUC value, U/L–day 1-7	1430 [947-2408]	1575 [977-3001]	1390 [915-1946]	.053
Peak ALT level, U/L	642 [381-1178]	756 [428-1424]	593 [346-905]	.021
ALT level AUC value, U/L–d 1-7	2459 [1545-3943]	2548 [1645-4647]	2323 [1429-3443]	.062
Total bilirubin level AUC value, μmol/L–d 1-7	15.1 [8.68-30.7]	15.6 [8.73-25.4]	14.1 [8.65-31.3]	.71
Total bilirubin level μmol/L–1 y	9.2 [6.8-13]	10 [7-13]	8.6 [6.7-12.1]	.24
GGT level AUC value, U/L–d 1-7	1446 [959-2213]	1648 [1166-2476]	1194 [849-1922]	<.001
GGT U/L–1 y	35 [24-73]	39 [26-86]	32 [21-64]	.033
AP level AUC value, U/L–d 1-7	947 [681-1352]	985 [749-1448]	925 [626-1212]	.031
AP level U/L–1 y	105 [81-146]	111 [80-153]	102 [81-137]	.52
INR AUC value–d 1-7	9.12 [8.36-10.3]	9.02 [8.24-10.4]	9.30 [8.43-10.2]	.22
eGFR d 1–7 nadir, mL/min/1.73 m^2 (n = 262)	41.1 [13.5-74.8]	45.0 [11.7-79.0]	36.8 [16.0-71.6]	.56
Platelet counts nadir, 10^9/L (n = 218)	42 [28-70]	47 [28-70]	40 [28-70]	.56
Additional outcome parameters				
Primary endpoint:	63 (24.0)	40 (30.5)	23 (17.6)	.014
EAD (Olthoff)				
Primary nonfunction	7 (2.67)	6 (4.58)	1 (0.76)	.12
MEAF score (0-10)	5.2 [3.6-6.9]	5.3 [3.6-7.0]	5.0 [3.6-6.8]	.66
L-GrAFT10 risk factor (n = 103)	–1.76 [–2.18 to (–1.12)]	–1.75 [–2.22 to (–1.16)]	–1.82 [–2.13 to (–1.09)]	.97
EASE score	–3.56 [–4.05 to (–2.92)]	-3.60 [–4.05 to (–2.95)]	-3.40 [–3.98 to (–2.92)]	.60
No of complications (n = 1811)				.035
CD 1-2	1484 (81.9)	685 (79.9)	799 (83.8)	
CD ≥3	327 (18.1)	172 (20.1)	155 (16.2)	
90-d mortality (CD = 5)	10 (3.8)	7 (5.3)	3 (2.3)	.20
No. of patients with:	107 (43.1)	47 (38.5)	60 (47.6)	.15
Minor complications (CD 1-2)				
Major complications (CD ≥3)	141 (56.9)	75 (61.5)	66 (52.4)	

(*continued on next page*)

Table 3 (*continued*)

Variables	Overall	Control	HOPE	*P*
No. of patients per complication type, n (%)				
- Hepatic artery thrombosis	5 (1.9)	4 (3.1)	1 (0.8)	.37
- Hepatic artery aneurysm	3 (1.1)	2 (1.5)	1 (0.8)	1
- Portal vein thrombosis	8 (3.1)	5 (3.8)	3 (2.3)	.72
- Hepatic vein thrombosis	3 (1.1)	1 (0.8)	2 (1.5)	1
- Any biliary complications	35 (13.4)	22 (16.8)	13 (9.9)	.10
- Biliary stenosis	24 (9.2)	14 (10.7)	10 (7.6)	.39
- Biliary fistula	15 (5.7)	10 (7.6)	5 (3.8)	.18
- Acute rejection	7 (2.7)	3 (2.3)	4 (3.1)	1
- Respiratory	19 (7.3)	13 (9.9)	6 (4.6)	.10
- Renal insufficiency	44 (16.8)	20 (15.3)	24 (18.3)	.51
1-year graft loss	33 (12.6)	17 (13.0)	16 (12.2)	.85
Liver-related graft loss due to:	14	9	5	
- Primary nonfunction	5	3	2	
- Hepatic artery thrombosis	5	4	1	
- NAS	3	2	1	
- Other[a]	1	0	1	
Patient-related graft loss due to:	19	8	11	
- Primary tumor recurrence	2	1	1	
- Secondary tumor growth	3	0	3	
- Opportunistic infection	7	4	3	
- Other[b]	7	3	4	
90-d cumulative CCI	47.6 [34.6-65.1]	49.5 [34.3-65.1]	46.1 [35.4-65.3]	.78
6-mo cumulative CCI	52.8 [37.2-71.3]	53.0 [37.2-69.4]	52.8 [38.2-72.4]	.61
Length of ICU stay, d	7 [4-13]	8 [4-14]	6.5 [4-10]	.27
Length of hospital stay, d	19.5 [14.0-31.0]	20 [14-31]	19 [14-31]	.74
1-yr retransplantation	9 (3.4)	6 (4.6)	3 (2.3)	.50
1-y graft survival[c]	229 (87.4)	114 (87.0)	115 (87.8)	.80
1-y patient survival[c]	237 (90.5)	119 (90.8)	118 (90.1)	.87
1-year NAS cholangiopathy (MRCP) (n = 172)	7 (4.1)	4 (4.9)	3 (3.3)	.71

Continuous variables are presented as median [interquartile range] and categorical variables as n (%).
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CCI, comprehensive complication index; EAD, early allograft dysfunction; EASE, early allograft failure simplified estimation; GGT, gamma-glutamyltransferase; HOPE, end-ischemic hypothermic oxygenated perfusion; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplantation; MEAF, model for early allograft function; MRCP, magnetic resonance cholangio-pancreatography; NAS, nonanastomotic stricture; RBC, red blood cell.

[a] Hepatic artery hemorrhage after biliary fistula.

[b] Cardiac arrest n = 2, cardiac insufficiency n = 2, centropontine myelinolysis n = 1, seizure n = 1, stroke n = 1.

[c] *P* value from log-rank test.

79 253.86] in the control group. There was no significant difference in costs between the 2 groups at 12 months (Table 4). The additional cost of the HOPE procedure was estimated at €5629.62 [5623.36-5637.62], mainly due to the cost of consumables (€5400).

4. Discussion

Although several randomized machine liver perfusion trials have been published to date, many of them included heterogeneous liver grafts and/or recipients, preventing strong

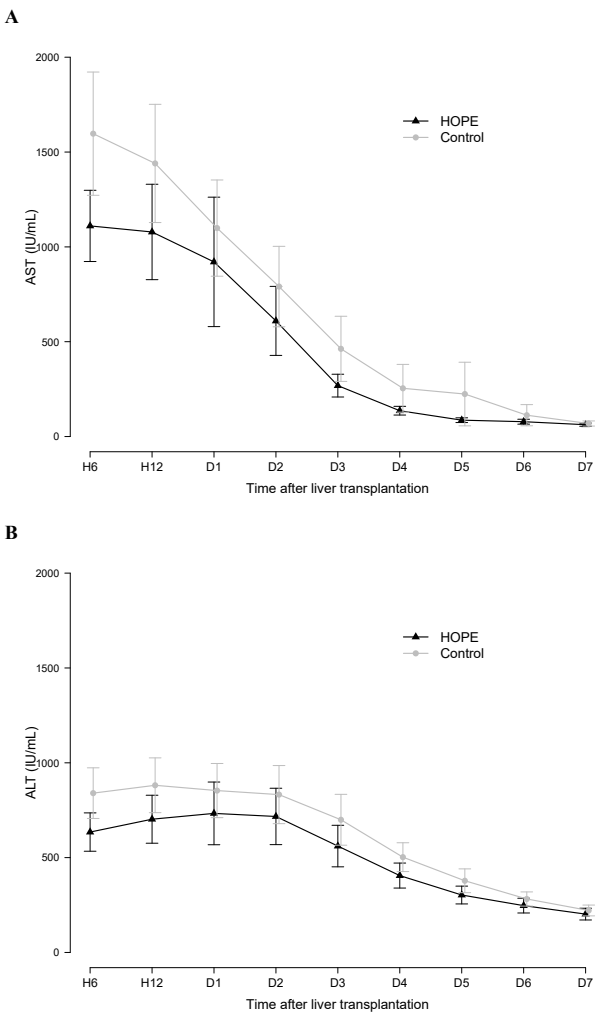

Figure 2. Serum aspartate aminotransferase (AST) levels (A) and alanine aminotransferase (ALT) levels (B) during the 7 postoperative days in the HOPE and control groups. Dots indicate mean values, and whiskers represent the 95% confidence intervals of the means. HOPE, end-ischemic hypothermic oxygenated perfusion.

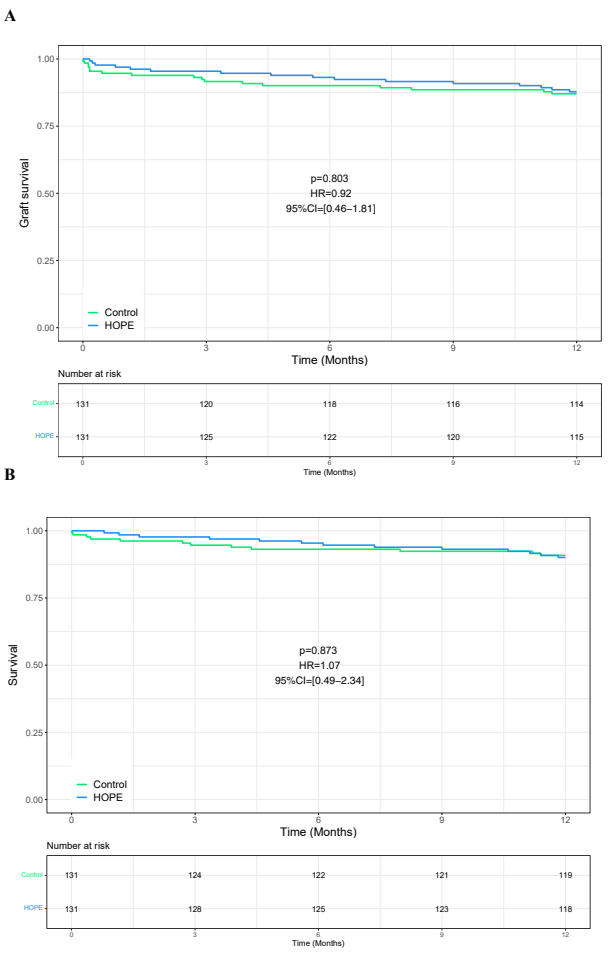

Figure 3. One-year graft (A) and patient (B) survival curves in the HOPE and control groups. CI, confidence interval; HOPE, end-ischemic hypothermic oxygenated perfusion; HR, hazard ratio.

conclusions from being drawn.[13-16,27,28] The present results were obtained from a multicenter RCT assessing the benefit of HOPE perfusion used before LT in a pure cohort of only ECD organs from DBD. No DCD donor was included in this study. The trial met its primary endpoint, demonstrating a significant reduction in EAD in the HOPE group and consequently improved outcomes in vulnerable recipients aged $\geq$60 years and with cold ischemia time $>$6 hours. Overall, the 1-year health care cost following transplantation was comparable between groups.

Although this trial dealing with HOPE had the highest sample size compared with other RCTs and reached its main endpoint, its clinical impact on morbidity and survival is moderate. However, even if it did not reach significance, only 1 patient (0.7%) suffered from PNF in the HOPE group compared with 6 patients (4.5%) in the control group. The total number of severe complications was lower in the HOPE group, and the 90-day mortality rate was more than half that of the control group (5.3% vs 2.3%, $P = .20$). The first explanation for this clinically moderate relevance is the very favorable outcomes in the control group with low rates of PNF, low morbidity and mortality, and excellent graft and patient survival. Second, favorable matching with mildly ill recipients and low MELD scores likely mitigated the potential positive effect of HOPE on ECD grafts. These findings can be explained by the caution of the transplant teams in avoiding matching ECD grafts in patients with high-MELD scores to optimize outcomes. Third, with a median of 6 hours, the cold ischemia time was short in both groups and was also likely associated with the good outcomes in the whole cohort of recipients. Indeed, in France, 1 of the allocation criteria is the distance between the procurement hospital and the transplant center, prioritizing short distances to keep cold ischemia time as short as possible.

Another potential confounding factor is the choice of inclusion criteria for ECD grafts. ECD criteria for DBD livers followed the ones described by EuroTransplant, which were restated in the 2016 European Association for the Study of the Liver Transplantation Clinical Practice Guidelines.[18,29] However, some of these ECD criteria in DBD donors are no longer considered relevant, as stated in the last 2024 ELITA consensus guidelines on deceased donor liver utilization and assessment.[30] Only graft

Table 4
Mean costs per patient at euro price year 2023 from the hospital perspective, within 12 months from liver transplantation.

Costs, mean [95% CI]	HOPE group (n = 131)	Control group (n = 131)	Difference[a] in costs
Overall	77 987.54 [72 948.57; 83 427.96]	72 748.5 [67 000.63; 79 253.86]	5,239.04 [–3275.81; 13 169.68]
Microcosting of the HOPE procedure	5629.62 [5623.36; 5637.62]	0 [0; 0]	5629.62 [5623.11; 5637.3]
Initial hospitalization for LT	64 092.51 [59 434.33; 68 560.8][b]	57 630.36 [52 944.43; 62 477.57]	6462.15 [–162.68; 13 160.67]
Other hospitalizations	11 709.83 [9460.48; 14 567.73]	11 772.13 [9447.47; 15 057.07]	–62.3 [–4016.21; 3,613.1]
Medical consultations	620.26 [562.92; 679.35]	593.26 [538.86; 649.06]	27 [–52.6; 104.94]
Laboratory and radiological examinations	541.64 [461.52; 642]	593.92 [505.1; 700.63]	–52.27 [–182.89; 82.9]

All costs were expressed in euros (€) at the 2023 price year and adjusted for inflation based on the French National Institute of Statistics and Economic Studies (INSEE) Consumer Price Indices of the health care products and services.
CI, confidence interval; HOPE, end-ischemic hypothermic oxygenated perfusion; LT, liver transplantation.

[a] Differences in bootstrapped mean costs were computed according to health economics standards (HOPE group – control group) to statistically compare groups. A significant statistical difference in costs is reached if the CI of the difference does not include zero.

[b] Additional costs of the HOPE procedure (evaluated using a microcosting approach) were included in the cost of the initial hospitalization for LT in the HOPE group.

steatosis ≥30% and age ≥70 years are currently considered as ECD, especially when they are combined with other risk factors in the recipient. In the present study, two-thirds of the donors had only 1 ECD, which was mainly age >65 years. As a reminder, DCD donors could not be included in this trial since the French organ procurement organizations impose that DCD donors be systematically reconditioned and assessed using in situ abdominal normothermic machine perfusion.[31]

HOPE is known to reduce the risk of nonanastomotic stricture after LT.[2] The present RCT is the only one including an objective assessment of the biliary tree at 1 year after LT by performing MRCP, regardless of symptoms and liver function tests. Sixty-six percent of the recipients underwent MRCP, showing no significant difference in 1-year nonanastomotic stricture between the HOPE and control groups (3.3% vs 4.9%, $P = .71$). Similarly, rates of 90-day biliary complications were not significantly different between the groups, even though they were less frequent in the HOPE group (9.9% vs 16.8%, $P = .1$). Most studies showing a protective effect of hypothermic perfusion on biliary complications are retrospective, with a lack of clear and uniform definition of biliary complications.[32,33] The only RCT reporting a clear protective effect of HOPE on biliary complications included only DCD donors submitted to consecutive warm and cold ischemia.[13] However, the authors only considered symptomatic biliary stenosis and did not perform systematic MRCP.

Besides the potential clinical benefits of machine perfusion, its economic outcomes should be discussed since liver machine perfusion is costly. Yet, accurate cost analyses are scarce in the literature. The present study is the first RCT to include a comprehensive cost analysis from a hospital perspective and over a time horizon of 12 months from surgery. The expenditure items included the surgical procedure using a prospective microcosting method, initial hospitalization for LT, and hospital resource consumption during the 12-month follow-up (ie, new hospitalizations, outpatient consultations, laboratory tests, and radiological examinations). Despite the additional costs of the perfusion procedure, including its consumables, this exhaustive cost analysis did not show any significant difference regarding the 12-month cost between the 2 groups, thereby providing valuable information for hospital decision makers to decide whether this technology should be implemented in routine practice. A recent RCT from Germany assessing HOPE before LT with ECD from DBD grafts reported similar findings,[15] but in a smaller cohort (n = 46) and using less exhaustive cost analysis, which was based only on age and CCI.[15,34] A multicenter retrospective study in the USA has recently focused on the impact of normothermic machine perfusion (NMP) on complications and costs after LT with DBD and DCD grafts.[17] Although organ acquisition/preservation was more costly with NMP, overall 90-day health care costs per LT were comparable between NMP and SCS groups. Other studies compared costs and effects after NMP vs SCS but were based on Markov models and not on an actual reporting of cost data.[35,36]

Four previous RCTs assessed the impact of HOPE perfusion of DBD grafts before LT compared with SCS, 2 of which included unselected DBD donors[14,27] whereas the 2 others focused on ECD-DBD[15,16] like the present study. They reported heterogeneous results. The study by Schlegel et al[14] included 85 patients in each arm and was negative regarding its primary endpoint, looking at the occurrence of major posttransplant complications. Yet a post hoc analysis showed fewer liver-related major complications in the HOPE group. Grąt et al[27] compared 26 patients in the dual HOPE arm with 78 patients in the SCS arm. Using the more modern MEAF score, they did not detect any significant difference in posttransplant EAD between groups. HOPE was associated with significantly lower MEAF score and lower CCI only when the donor risk index was >1.70. The study by Czigany et al[15] was the first to focus only on ECD-DBD grafts, comparing 23 patients in each arm. Serum peak ALT level was the primary endpoint and was halved after HOPE, which was also associated with a significant reduction in 90-day complications and length of stays compared with SCS. There was only a trend toward reduced EAD in the HOPE group. In a long-term follow-up report, they showed that HOPE reduced late-onset morbidity and improved long-term graft survival.[37] Finally, the RCT by Ravaioli

et al[16] compared 55 patients in each arm undergoing transplantation of ECD-DBD grafts after HOPE or SCS. The trial met its primary endpoint, demonstrating a reduction in EAD in the HOPE group and consequently an improved 1-year graft survival.

The present results, combined with those from previous RCTs, allow us to draw cautious conclusions about the use of end-ischemic HOPE in DBD grafts. First, conventional DBD grafts do not seem to benefit from HOPE, especially in the case of matching with mildly ill recipients with low MELD scores. HOPE seems to provide beneficial effects on outcomes after LT when ECD grafts are used in otherwise high-risk recipients at risk or after long cold ischemia time. Some additional investigations are still mandatory to determine the best indications of HOPE in LT.

One limitation of the trial is the EAD definition used according to Olthoff et al.[7] Although it is not perfect because of its binary aspect, it was the only EAD criterion at the time of the study with enough results from previous trials to allow the calculation of a robust sample size. The other scores, such as MEAF, L-GRAFT, and EASE, were not included in the original study design because they were not validated at the time of the study onset. Not surprisingly, there was no significant difference in those more recent scores between the 2 groups since the trial was not adequately powered. A center effect on outcomes cannot be ruled out since the volume of LT was heterogeneous among centers. However, it reflects real life in many countries, and the stratification according to center allowed a good balance between the 2 groups within centers.

In conclusion, we confirm that HOPE improves outcomes in LT with ECD organs from DBD by reducing EAD without significantly increasing costs 12 months after LT. Although it provides a moderate clinical impact on morbidity and survival in recipients with low MELD scores, older recipients with long cold ischemia time might benefit the most.

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Authors contributions

M.L.: Conceptualization, Methodology, Investigation, Resources, Writing Original draft, Writing - review & editing, Visualization, Supervision, Funding Acquisition.; K.M.: Validation, Writing - review & editing, Investigation, Resources, Supervision; M.-A.A., R.A., F.R., M.R., K.B., A.C., E.B., E.S., O. Scatton, E.G., M.C., S.D., O. Soubrane, F.F., and P.B.: Investigation, Resources; V.H.: Validation, Investigation, Resources; P.G., J. A.: Methodology, Validation, Investigation, Resources; S.P., S. T., M.M.: Validation, Project administration, Data Curation, Supervision; P.P.: Methodology, Validation, Formal analysis, Data Curation, Writing - Review & Editing, Visualization; J.-Y.M.: Conceptualization, Methodology, Investigation, Resources, Writing review & editing, Visualization, Supervision.

Declaration of competing interest

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

Data availability

The data used to support the findings of this study are included and available within the article.

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