Original Article

Hypothermic oxygenated machine perfusion does not increase the risk of infection after liver transplantation: a retrospective cohort study

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Background: Liver transplantation (LT) is a crucial treatment for end-stage liver disease, but the limited organ supply has led to the use of extended criteria donors (ECD). The implementation of dynamic preservation techniques like hypothermic oxygenated machine perfusion (HOPE) is crucial in improving outcomes for ECD grafts. However, graft contamination and infection are a concern. This study aimed to evaluate the risk of infections within 10 days from LT between HOPE and static cold storage (SCS) groups and postoperative complications.

Methods: A retrospective cohort study was conducted, including LT recipients transplanted at a single-center from March 2016 to June 2023. Patients were divided into HOPE and SCS groups, and propensity score matching was used to select comparable cohorts. Data on patient and donor characteristics were analyzed.

Results: After propensity score matching, a cohort of 370 (HOPE, n=185; SCS, n=185) patients was selected for analysis. The study found no significant differences in the rate of clinically relevant infections, microbiological positive samples, or donor-derived infections within 10 days between HOPE and SCS groups. Postoperative outcomes, as well as patient and graft survival, were also similar between the two groups. The study showed that HOPE is a feasible and safe approach, with a comparable risk of infection.

Conclusions: The study results indicate that HOPE use in LT does not increase the risk of infection and is associated with similar patient and graft survival outcomes compared to SCS. These findings confirm the safety and efficacy of HOPE in LT and its potential to expand the donor pool without compromising recipient outcomes.

Keywords: Liver transplant; infections; hypothermic oxygenated machine perfusion (HOPE); mortality; hypothermic

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Introduction

Liver transplantation (LT) represents a life-saving treatment for patients with end-stage liver disease, but it is limited by organ supply (1,2). Utilization of organs from so-called extended criteria donors (ECD), including but not limited to those whose death has been determined by circulatory criteria [donation after circulatory death (DCD)], has been considered to expand donor pool, highlighting the necessity to improve organ preservation when these organs are used, to avoid a detrimental impact on LT outcomes (3-5). To overcome the limitations of static cold storage (SCS) (6), dynamic preservation techniques, such as normothermic machine perfusion (NMP) and hypothermic oxygenated machine perfusion (HOPE), are being widely implemented in liver transplant centers around the world (4,7).

During HOPE, an acellular perfusate is actively oxygenated and recirculated through the liver graft at low (4–10 ℃) temperature, reducing mitochondrial injury during preservation and resulting in a lower release of reactive oxygen species upon graft reperfusion (8,9). In clinical LT, HOPE is most frequently applied after a period of SCS (end-ischemic approach), and its use has been associated with a lower incidence of ischemic cholangiopathy and postoperative complications, and improved graft survival (7-17). At Azienda Ospedaliero Universitaria (AOU) City of Health and Sciences, HOPE was introduced in March 2016 and has been implemented as the routine preservation technique for ECD grafts since November 2017. A scarcely investigated aspect of HOPE is whether its application is associated with an increased risk of graft contamination and recipient infection. Donor-derived infections might potentially be transmitted to the recipient through the use of preservation fluid (PF) or perfusion fluid (PRF) (18). The reported rate of bacteria isolation on PF cultures (PFCs) ranges between 28.9% and 98% (15,19-24). However, the incidence of PF-related infection (PF-RI) is lower, with a range of 7.4% to 10%. Nevertheless, there has been a significant mortality associated with PF-RI, with a reported mortality rate up to 35% (20,21,25). In theory, any graft manipulation and exposure may result in an increased risk of contamination. In SCS, liver is packaged in a sterile environment and the possibility of contamination during preservation is ideally nihil, except when it is unpacked for backtable preparation and then moved to the recipient for implantation. When HOPE is applied, this exposure is significantly prolonged during vessel cannulation and connection to the machine perfusion device. Furthermore, as all commercially available HOPE devices utilize an open circuit, pathogens present on the liver surface could easily contaminate PRF and spread through liver microcirculation. Bacterial overgrowth in the perfusate, potentially leading to recipient severe infections, is a well-known issue in NMP (26,27). Endo *et al.* recently reported no microbial transmission in a series of 52 patients transplanted with a HOPE-treated graft (27). Perfusate contamination leading to recipient infection has been anecdotally reported after HOPE (28), mostly due to *Enterobacteriales* (22,24) having been isolated on both the HOPE perfusate and on the blood culture of the recipient. However, a formal assessment of the risk of recipient infection associated with HOPE is currently lacking.

Thus, the aim of this study was to evaluate the risk of infections within 10 days from LT between HOPE and SCS groups. In addition, the study aimed to assess outcomes regarding postoperative complications and patient and graft

Highlight box

Key findings

- Hypothermic oxygenated machine perfusion (HOPE) in liver transplantation (LT) did not increase the risk of infection within 10 days post-transplantation.
- Despite higher donor risk profile, postoperative and survival outcomes were similar between HOPE and static cold storage (SCS) groups.
- The study supports the safety and efficacy of HOPE in LT and its potential to expand the donor pool without compromising recipient outcomes.

What is known and what is new?

- LT using extended criteria donors (ECD) has highlighted the need for improved organ preservation techniques.
- HOPE has shown promise in reducing complications for ECD grafts.
- It is uncertain whether the use of HOPE in LT is associated with an increased risk of recipient infection.
- This manuscript adds evidence demonstrating that HOPE does not increase the risk of infection after LT and supports its potential to expand the donor pool without compromising recipient outcomes.

What is the implication, and what should change now?

- This study shows that the use of HOPE in LT does not increase the risk of infection and is associated with similar patient outcomes compared to SCS, despite its preferential use for grafts from extended-criteria donors. While specific antibiotic prophylaxis is not recommended in recipients of a HOPE-treated liver, obtaining cultures of HOPE perfusate, ideally collected at the end of machine perfusion, could inform the treatment of the anecdotal cases of donor-derived recipient infection.

survival. We present this article in accordance with the STROCSS reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-552/rc).

Methods

Study design

We performed a single-center retrospective cohort study including all consecutive adult (≥18-year-old) LT recipients transplanted at AOU City of Health and Sciences between March 2016 and June 2023 to compare the risk of early, i.e., within 10 days from LT, infection in recipients of grafts treated by HOPE *vs.* SCS. Data was collected from the Liver Transplant Unit at Molinette Hospital, a primary care setting, City of Health and Sciences of Turin, Turin, Italy. The study was conducted according to the principles of the Declaration of Helsinki and its subsequent amendments and the Declaration of Istanbul and was approved by the Institutional Ethics Committee of the City of Health and Sciences of Turin (CET resolution nr. 506/2021). Informed consent was waived because of the retrospective nature of the study and the fact that the analysis used anonymous clinical data.

The primary endpoint was to report the incidence of clinically relevant infections presenting within 10 days after LT. Secondary endpoints were to describe: the major differences at baseline between the two groups, positive microbiological isolates within 10 days from LT, parameters of graft function after LT, donor-derived infections within 10 days. Final outcomes were also reported, including postoperative complications, and patient and graft survival.

For each patient, demographic and clinical data, including donor features and procedural variables, were collected from electronic medical records. We collected results of PRF cultures obtained at the start of backtable preparation, as well as all positive microbiological results from urine, bile, blood, and respiratory samples obtained within 10 days from LT. Microbiological data were matched with clinical data to define clinically relevant infections.

Given their higher risk of post-LT infection, we excluded patients undergoing redo-LT or combined transplants, as well as those transplanted for acute liver failure, those who were admitted to hospital before LT, and those treated with temporary packing and delayed abdominal wall closure. Recipients of a graft treated by either NMP or normothermic regional perfusion were also excluded. Given the systematic use in DCD donors of normothermic regional perfusion (29,30), which could also potentially increase the risk of graft contamination, only recipients of DBD grafts were included. Livers from donors with documented bacteremia or bowel injury during procurement were excluded. To limit confounding due to pre-LT patient characteristics and surgical events, 1:1 propensity-score matching was used to select two cohorts of patients with comparable risk of infection.

Patient management

Liver procurement, preservation, and transplantation were performed as previously described (10). Briefly, liver grafts were cold flushed at procurement with Celsior solution (IGL, Lissieux, France) and transported under SCS to AOU City of Health and Sciences. Upon arrival, the liver was unpacked, and a sample of perfusion used during SCS was collected before backtable preparation and sent for microbiological examination. Afterwards, livers in the HOPE group underwent dual HOPE using the LiverAssist device (XVIVO, Gothenburg, Sweden) until the end of recipient hepatectomy, with a target time of ≥2 hours, whereas livers in the SCS group were kept in static hypothermia until the recipient was ready for implantation.

Immunosuppression was based on induction by basiliximab (20 mg intraoperatively and on postoperative day 4th), tacrolimus (trough level 6–10 ng/mL during the first 10 postoperative days), steroids and mycophenolate mofetil [500–1,000 mg twice daily (bid)]. Immunosuppression protocol did not change over study period. Antibiotic prophylaxis with piperacillin/tazobactam was administered regardless of HOPE use for 72 hours unless otherwise indicated based on donor or recipient cultures. Antifungal prophylaxis with amphotericin B was selectively administered according to AOU City of Health and Sciences's protocol (31).

Microbiological diagnosis methods

To detect aerobic and anaerobic bacteria, 2–10 mL of PRF is cultured using BACT/ALERT VIRTUO Plus (Biomerieux, Marcy-l'Étoile, France) and incubated up to 5 days. In case of bacteria growth, an amount of 10 µL fluid are cultured on blood, MacConkey, and Centers for Disease Control and Prevention anaerobic blood agar (CDC). Bacteria species identification was performed using the matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) technology (Bruker, Bremen, Germany). Antimicrobial susceptibility test was carried out with the MicroScan WalkAway plus (Beckman Coulter,

Brea, CA, USA) using Pos Combo 33, Neg Combo 83, and MDR MIC 1 panels for gram-positive and gram-negative, respectively. Sensibility of anaerobic organisms is tested using the gradient method (E-Test, Biomerieux). After overnight incubation, susceptibility is interpreted according to EUCAST indications (32).

Definitions

Septic shock was defined according to the SESPIS III criteria (33). Blood stream infection (BSI) was defined as a laboratory-confirmed bloodstream infection (LCBI) that was not secondary to an infection at another body site according to the National Healthcare Safety Network (NHSN) (34). Urinary tract infection was defined according to CDC (35) as a positive urine culture associated with symptoms of lower (dysuria, strangury, urinary urgency) or upper urinary tract infection with or without fever or associated bloodstream infection. Diagnosis of pneumonia was based on symptoms and signs of an acute lower respiratory tract infection, which was confirmed by a chest X-ray showing new shadowing that was not due to other causes (36). Intraabdominal infections (IAIs) were defined as a variety of pathological conditions involving intra-abdominal organs, including inflammation of single organs, peritonitis (primary, secondary, tertiary) as well as intra-peritoneal, retroperitoneal, and parenchymal abscesses (37). An infection fulfilling at least one of the aforementioned definitions was considered as clinically significant. Possible donor-derived infections were defined when all following surrogate criteria were satisfied: (I) identical species between the microorganisms isolated from the donor and those isolated from the recipient; (II) identical antibiotic susceptibility patterns of the isolated microorganisms; and (III) presence of clinical signs of infection in the recipient (37-41).

ECD donors were defined as those meeting at least on the following characteristics: age >65 years, BMI >40 kg/m^2, macrovesicular steatosis >30%, intensive care unit (ICU) stay ≥7 days, sodium >165 mEq/L (42). Macrovesicular steatosis was defined as the percentage of hepatocytes containing large fat droplets displacing the nucleus and assessed according to Neil *et al.* (43). Postreperfusion syndrome was defined according to Aggarwal *et al.* (44,45). Early allograft dysfunction (EAD) and the liver graft assessment following transplantation (L-GrAFT) score were defined according to the original publications (46,47). Postoperative complications were graded according to the Clavien-Dindo classification (48) and the comprehensive complication index (CCI) (49).

Statistical analysis

Categorical and continuous variables are reported as count (percentage) and median [interquartile range (IQR)]. Study groups were compared using Chi-squared, Fisher's exact, and non-parametric Mann-Whitney tests, as appropriate. Significance was set as P value <0.05. To limit confounding due to baseline recipient characteristics, donor features and operational variables, propensity score matching was used to select two comparable groups. Individual propensity scores were calculated based on the following variables: Model for End-Stage Liver Disease (MELD)-Na, presence of moderate or severe ascites, donor age, LT operation time, and number of packed red blood cells transfused during LT operation. Comparability between groups was assessed by absolute standardized mean differences. Analyses and data visualization were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

During study period, 1,062 adult LTs were performed at AOU City of Health and Sciences. After exclusion of 353 patients meeting exclusion criteria, 709 patients remained, of which 186 received a liver treated by HOPE and 523 preserved by SCS. Following, 1:1 propensity score matching, a cohort of 370 patients was selected (HOPE, n=185; SCS, n=185) for analysis (*Figure 1*).

Good balance between groups was confirmed by absolute standardized mean differences <0.15 (*Figure 2*) for all variables used to calculate propensity scores.

However, due to the preferential use of HOPE for livers from elderly donors, donor age was still higher is the HOPE group (76.3 *vs.* 74.3 years, P=0.03) (*Table 1*).

Baseline characteristics of recipients were described in *Table 1*. Recipient characteristics were comparable between study groups, with the exception that recipients in the HOPE group were older (60.8 *vs.* 57.8 years, P<0.01). Due to the selection process, two groups of low-risk patients were selected, characterized by a MELD-Na of 12 in both groups and a high prevalence of LT performed for HCC (67.0% and 64.3% in the HOPE and SCS groups, respectively). Expectedly, differences between study groups mainly concerned donor features. Besides being older, donors in the HOPE group had higher BMI (26.9 *vs.* 24.9 kg/m^2, P<0.01) and their livers had a higher percentage of macrovesicular steatosis (2.0% *vs.* 1.0%, P=0.02). As an effect of higher donor age, also D-MELD score (donor

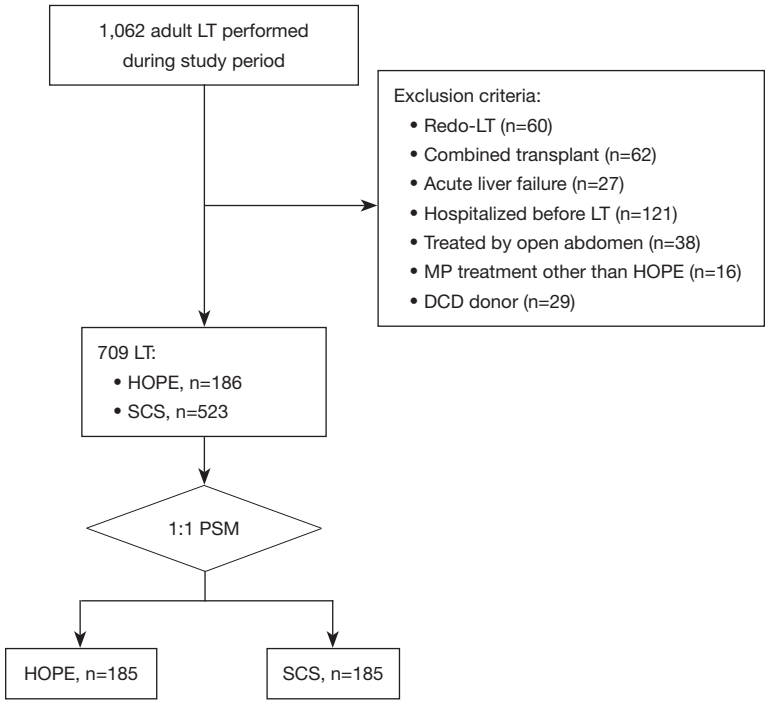

Figure 1 PRISMA flowchart for the selected cohort. DCD, donation after circulatory death; HOPE, hypothermic oxygenated machine perfusion; LT, liver transplantation; MP, machine perfusion; PSM, propensity score matching; SCS, static cold storage.

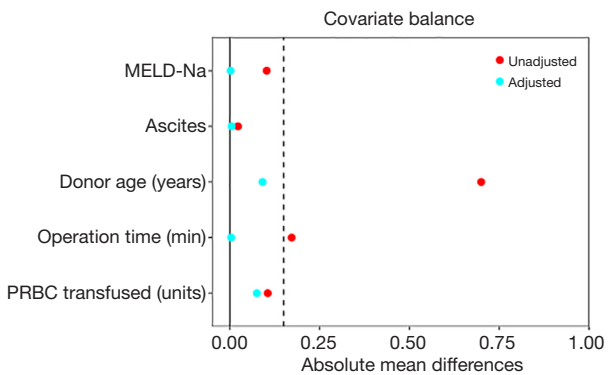

Figure 2 Variable balancing between HOPE and SCS. Red and blue dots show absolute standardized mean differences in the unmatched and matched cohort, respectively. After propensity score matching, all absolute standardized mean differences were below the 0.15 threshold. HOPE, hypothermic oxygenated machine perfusion; MELD, Model for End-Stage Liver Disease; PRBC, packed-red blood cell; SCS, static cold storage.

age × MELD) was higher in the HOPE group (869 *vs.* 750, P=0.04). Due to the logistics of LT when HOPE was used, total preservation time was higher in the HOPE group (506 *vs.* 437 min, P<0.01), whereas SCS time was shorter (362 *vs.* 437 min, P<0.01) (*Table 1*). Baseline patient characteristics in the unmatched cohort is reported in Table S1.

Regarding PFs isolates, the percentage of positive PFCs was almost identical between study groups [HOPE, n=148 (80.0%); SCS, n=149 (80.5%), P>0.99] (*Table 2*). The rate of polymicrobial PF infection was also comparable (20.0% *vs.* 25.4%, P=0.26). Most PFCs grew methicillin susceptible coagulase-negative *Staphylococci*, which were isolated in 44.3% and 50.3% of cultures in the HOPE and SCS group, respectively. Other frequently isolated germs were methicillin-resistant coagulase-negative *Staphylococci* (7.6% *vs.* 7.0%, P>0.99), *Escherichia* species (11.4% *vs.* 7.6%, P=0.29), and *Klebsiella spp* (7.0% *vs.* 4.9%, P=0.51) (*Figure 3*). There were no significant differences in the rate of PF infection for any of the isolated germs.

Regarding infections, overall 36 patients had a positive microbiological isolate within 10 days after liver transplant. Of which, 19 had a clinically significant infection, according to previous mentioned definitions. The overall rate of microbiological positive samples (11.4% *vs.* 8.1%, P=0.38) and clinically significant (5.4% *vs.* 4.9%, P>0.99) infections was comparable between study groups. Three patients (HOPE, n=2; SCS, n=1) presented with a documented donor-derived infection. Presence of infection after

Table 1 Baseline patient characteristics

Characteristics	Overall (n=370)	SCS (n=185)	HOPE (n=185)	P	ASMD
Rec. age (years)	59.6 [54.1, 64.5]	57.8 [53.7, 62.7]	60.8 [55.5, 66.0]	<0.01	–
Gender (male)	279 (75.4)	140 (75.7)	139 (75.1)	>0.99	–
Rec. BMI (kg/m^2)	25.3 [22.8, 27.7]	25.1 [22.3, 27.7]	25.6 [23.1, 27.7]	0.35	–
Indication				0.24	–
Viral hepatitis	187 (50.5)	95 (51.4)	92 (49.7)		
Alcohol	64 (17.3)	26 (14.1)	38 (20.5)		
Cholestatic	24 (6.5)	16 (8.6)	8 (4.3)		
MASLD	18 (4.9)	8 (4.3)	10 (5.4)		
Autoimmune	9 (2.4)	3 (1.6)	6 (3.2)		
Other	68 (18.4)	37 (20.0)	31 (16.8)		
HCC	243 (65.7)	119 (64.3)	124 (67.0)	0.66	–
MELD	11.0 [9.0, 15.0]	11.0 [8.0, 15.0]	11.0 [9.0, 15.0]	0.53	–
MELD-Na	12.0 [9.0, 15.8]	12.0 [9.0, 15.0]	12.0 [9.0, 16.0]	0.96	0.03
Rec. creatinine (mg/dL)	0.8 [0.7, 1.0]	0.8 [0.7, 1.0]	0.8 [0.7, 1.0]	0.68	–
Dialysis pre-LT†	1 (0.3)	1 (0.5)	0 (0.0)	>0.99	–
Prev. abdominal surgery†	121 (32.7)	59 (31.9)	62 (33.5)	0.77	–
Life support†	2 (0.5)	1 (0.5)	1 (0.5)	>0.99	–
Ascites†	121 (32.7)	62 (33.5)	59 (31.9)	0.82	0.03
Encephalopathy†	52 (14.1)	25 (13.5)	27 (14.6)	0.88	–
Donor age (years)	75.3 [63.8, 81.0]	74.3 [64.8, 79.0]	76.3 [63.6, 82.7]	0.03	0.10
Donor BMI (kg/m^2)	25.9 [23.1, 29.1]	24.9 [23.0, 27.8]	26.9 [23.4, 30.4]	<0.01	–
Macrosteatosis (%)	2.0 [0.0, 7.0]	1.0 [0.0, 5.0]	2.0 [0.0, 10.0]	0.02	–
Graft weight (gr)	1,370 [1,172, 1,627]	1,400 [1,190, 1,640]	1,350 [1,150, 1,610]	0.41	–
ECD	305 (82.4)	152 (82.2)	153 (82.7)	>0.99	–
D-MELD	798 [617, 1,087]	750 [596, 1,041]	869 [666, 1,132]	0.04	–
Total pres. time (min)	477 [424, 532]	437 [388, 489]	506 [467, 564]	<0.01	–
SCS time (min)	399 [337, 461]	437 [388, 489]	362 [318, 413]	<0.01	–
HOPE time (min)	–	–	132 [120, 180]	–	–
Operation time (min)	355 [297, 412]	352 [297, 415]	357 [298, 412]	0.85	0.02
PRBC (units)	2.0 [0.0, 5.0]	2.0 [0.0, 6.0]	2.0 [0.0, 5.0]	0.42	0.09

Data are expressed as number (percentage) or median [IQR]. †, previous abdominal surgery indicates patients with a history of major abdominal surgery before transplant; the need for dialysis or life support, as well as the presence of encephalopathy and ascites were evaluated in the 2 weeks preceding transplant. ASMD, absolute standardized mean difference; BMI, body mass index; D-MELD, donor age × MELD; ECD, extended-criteria donor; HCC, hepatocellular carcinoma; HOPE, hypothermic oxygenated machine perfusion; IQR, interquartile range; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; pres., preservation; prev., previous; PRBC, packed-red blood cell; rec., recipient; SCS, static cold storage.

Table 2 PF isolates

Microbiological characteristics of PF cultures	SCS (n=185)	HOPE (n=185)	P
Positive PF	149 (80.5)	148 (80.0)	>0.99
Polymicrobial infection	47 (25.4)	37 (20.0)	0.26
Gram-positive	122 (65.9)	112 (60.5)	0.33
Methicillin-susceptible coagulase-negative *Staphylococci*	93 (50.3)	82 (44.3)	0.30
Methicillin-resistant coagulase-negative *Staphylococci*	13 (7.0)	14 (7.6)	>0.99
Ampicillin susceptible *Enterococci*	8 (4.3)	10 (5.4)	0.81
Streptococcus spp	8 (4.3)	3 (1.6)	0.22
Methicillin-susceptible *S. aureus*	4 (2.2)	2 (1.1)	0.68
Methicillin-resistant *S. aureus*	3 (1.6)	0 (0.0)	0.25
Gram-negative	37 (20.0)	43 (23.2)	0.53
E. coli	14 (7.6)	21 (11.4)	0.29
Klebsiella spp	9 (4.9)	13 (7.0)	0.51
Acinetobacter spp	3 (1.6)	3 (1.6)	>0.99
Fungi	9 (4.9)	9 (4.9)	>0.99
Candida albicans	7 (3.8)	5 (2.7)	0.77
Candida non-albicans	2 (1.1)	5 (2.7)	0.45

Data are expressed as number (percentage). *E. coli, Escherichia coli*; HOPE, hypothermic oxygenated machine perfusion; PF, preservation fluid; *S. aureus, Staphylococcus aureus*; SCS, static cold storage.

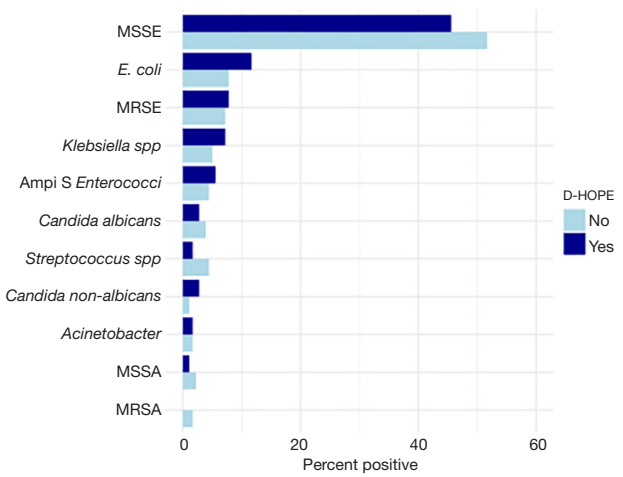

Figure 3 Positive isolates from PFCs. Ampi S, ampicillin susceptible; D-HOPE, dual hypothermic oxygenated machine perfusion; *E. coli*, *Escherichia coli*; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant coagulase negative *Staphylococci*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MSSE, methicillin-sussceptible coagulase negative *Staphylococci*; PFC, preservation fluid culture.

LT negatively impacted patient survival, this effect was less evident when the analysis was restricted to patients presenting with BSI only (*Figure 4*).

Other clinical outcomes were comparable between study groups, with the exception that patients in the HOPE groups have a lower peak of aspartate aminotransferase (AST) (870 *vs.* 1,151 IU/L, P<0.01) and alanine aminotransferase (ALT) (449 *vs.* 692 IU/L, P<0.01) and lower CCI at discharge from hospital (20.9 *vs.* 22.6, P=0.02) (*Table 3*). Patient and graft survival were not influenced by preservation modality (*Figure 4*).

Discussion

While LT has witnessed remarkable advancements over the past 60 years, preservation methods have only recently experienced significant improvement. Given the escalating risks associated with an increasing proportion of lower quality donor livers, traditional SCS preservation may not be sufficient. The recent introduction of dynamic preservation by oxygenated machine perfusion has been a

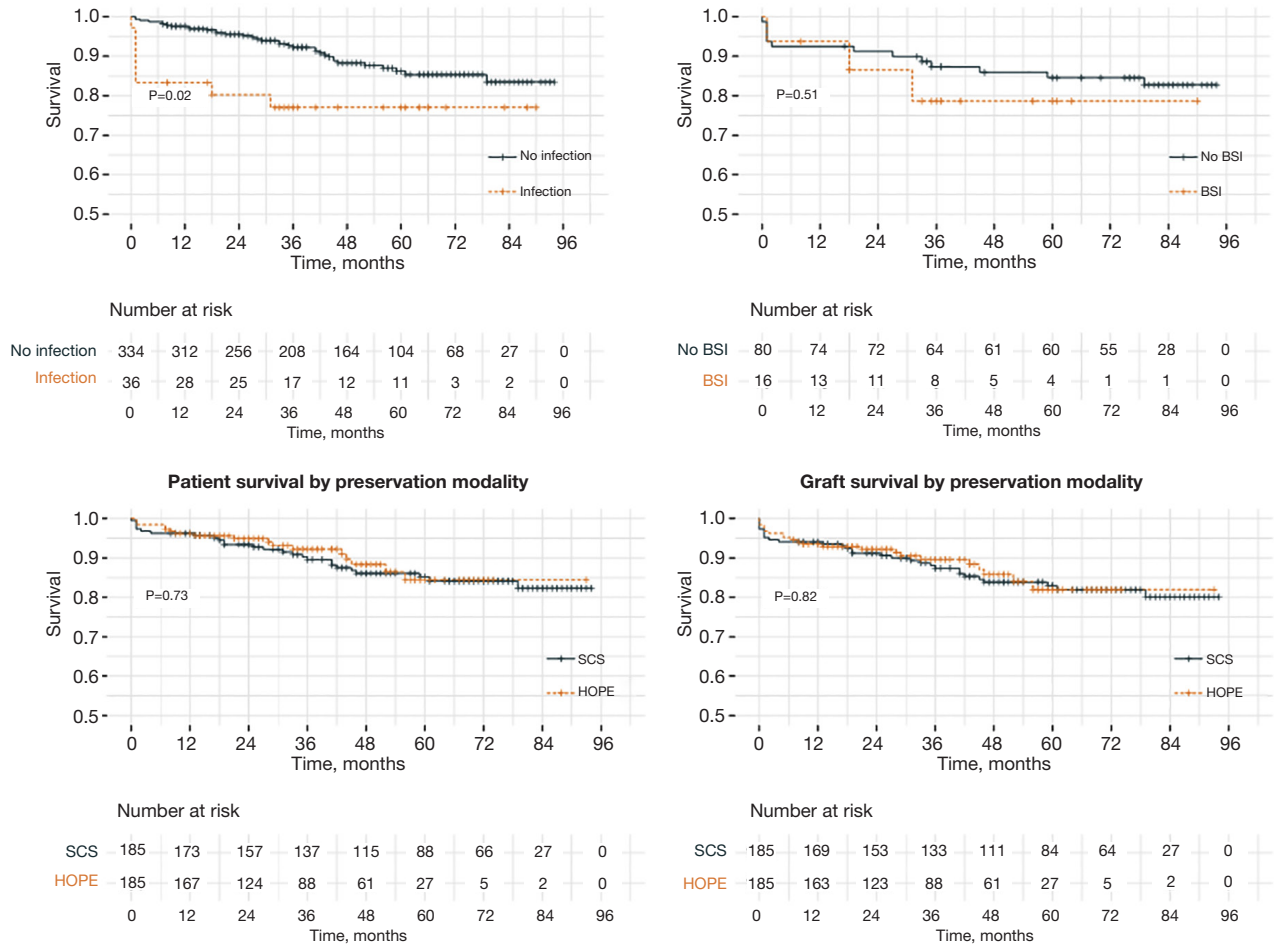

Figure 4 Patient and graft survival by preservation modality. BSI, blood stream infection; HOPE, hypothermic oxygenated machine perfusion; SCS, static cold storage.

revolution in the field, marking a substantial breakthrough in LT. Accordingly, machine perfusion of donor livers evolved in the last 10 years from a pure experimental approach to clinical implementation in an increasing number of transplant centers worldwide (50). HOPE has been associated with lower incidence of ischemic cholangiopathy, postoperative complications, and improved graft survival. Infectious complications are a major concern after liver transplant and are usually associated with higher mortality and graft failure. However, limited data are available about the infection risk associated with HOPE use in LT. The low but actual risk of donor-derived infection in patients receiving a liver graft treated by NMP is well documented (51,52), with the risk of graft contamination appearing proportional to the duration of machine perfusion (26). Although HOPE use has been investigated by a number of previous RCTs (7,12,13,15,16), recipient infection has been poorly explored, with data on perfusate cultures and results of microbiological examinations in the recipient lacking. Endo *et al.* (27) analyzed a series of 90 patients receiving a machine perfusion-treated graft (NMP, n=31; HOPE, n=59) reporting one case of *Escherichia coli* (*E. coli*) infection in a recipient of a NMP graft, whereas no infections were reported after HOPE. This study, however, lacked a control group and did not account for potential donor and recipient confounding factors. Our study, in contrast with previous literature, was designed to assess the comparative risk of preservation-related infection in HOPE *vs.* SCS, excluding high-risk patients and accounting for potential confounders.

Table 3 Clinical outcomes

Outcomes	Overall (n=370)	SCS (n=185)	HOPE (n=185)	P
Microbiological positive samples ≤10 days from LT	36 (9.7)	15 (8.1)	21 (11.4)	0.38
Clinically significant infections ≤10 days from LT	19 (5.1)	9 (4.9)	10 (5.4)	>0.99
With sepsis	5 (1.4)	3 (1.6)	2 (1.1)	>0.99
Donor-derived infection	3 (0.8)	1 (0.5)	2 (1.1)	>0.99
Severe PRS	48 (13.0)	27 (14.6)	21 (11.4)	0.43
AST peak (IU/L)	988 [611, 1,699]	1,151 [720, 1,794]	870 [504, 1,367]	<0.01
ALT peak (IU/L)	616 [343, 987]	692 [469, 1,039]	449 [278, 905]	<0.01
EAD	91 (25.6)	47 (25.4)	44 (23.8)	>0.99
L-GrAFT score	–2.0 [–2.4, –1.5]	–2.0 [–2.4, –1.5]	–1.9 [–2.3, –1.4]	0.24
L-GrAFT score (risk estimate)	12.2 [8.3, 18.3]	11.4 [8.2, 17.6]	13.0 [8.9, 19.6]	0.24
Severe AKI	89 (24.1)	44 (23.8)	45 (24.3)	0.98
Renal replacement therapy	10 (2.7)	3 (1.6)	7 (3.8)	0.34
Early rejection	29 (7.9)	18 (9.7)	11 (5.9)	0.25
Clavien ≥3 complications	45 (12.4)	26 (14.1)	19 (10.3)	0.37
Hospital CCI	20.9 [8.7, 29.6]	22.6 [8.7, 29.6]	20.9 [8.7, 29.6]	0.02
ICU stay (days)	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	0.93
Admission days	10.0 [8.0, 15.0]	11.0 [8.0, 15.0]	10.0 [8.0, 15.0]	0.46
Early graft loss	13 (3.7)	10 (5.4)	3 (1.6)	0.12

Data are expressed as number (percentage) or median [IQR]. Clinical significant infections: suspected origin of infection BSI (n=16), pneumonia (n=3), UTI (n=3), and IAI (n=9). AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSI, blood stream infection; CCI, comprehensive complication index; EAD, early allograft dysfunction; HOPE, hypothermic oxygenated machine perfusion; IAI, intraabdominal infection; ICU, intensive care unit; IQR, interquartile range; L-GrAFT, liver graft assessment following transplantation; LT, liver transplantation; PRS, postreperfusion syndrome; SCS, static cold storage; UTI, urinary tract infection.

In our study, recipients' characteristics were comparable in the two groups, with the exception that HOPE recipients were significantly older than SCS recipients. Due to the selection process, two groups of low-risk patients were selected, characterized by a MELD-Na of 12 in both groups. Due to the preferential allocation of ECD livers to low-MELD patients, in which the indication for LT is frequently HCC, prevalence of HCC was rather high in both groups (67.0% and 64.3% in the HOPE and SCS groups, respectively). Although our methodology mitigated selection bias (*Figure 2*), differences in donor features persisted due to the preferential use of HOPE in livers from ECD. As a consequence, in the HOPE group donors were significantly older, had a significant higher BMI, and the degree of macrovesicular steatosis was higher. Due to older donor age, also D-MELD was higher in the HOPE group. While this might have theoretically increased the risk of graft dysfunction and therefore infection in the HOPE group, clinical outcomes were comparable between the two groups. Notably, HOPE use was associated with a lower transaminase peak after LT and with less postoperative complication, as suggested by the lower CCI. Additionally, the rate of early allograft loss was reduced to less than a third in the HOPE group, although this difference did not reach statistical significance (5.4% *vs.* 1.6%, P=0.12). Overall, this is in keeping with the beneficial effects of HOPE on graft preservation (9-17) and suggests that its use compensated for the higher-risk donor profile in the HOPE group.

In terms of PF samples, the percentage of positive

cultures were almost identical between the two groups (80%) and like those reported in literature, ranging from 28.9% to 98%. Coagulase-negative *Staphylococci* were reported in almost half of the cases, as frequently reported in the literature (53). In the recipients, rates of positive microbiological samples, type of isolates as well as clinically relevant infections and donor-derived infections within 10 days did not show any statistically significant difference between study groups, suggesting that HOPE is a feasible and safe approach in LT, with similar risk of infections as compared to SCS. To the best of our knowledge, this is the first study describing the risk of infection in HOPE considering potential confounders.

We further evaluate patient survival according to infections, BSI, and preservation modality. Kaplan-Meier curves showed that survival was significantly higher in patients who did not develop infections compared to those who developed clinically relevant infections. However, if we evaluate the survival rate in patients with BSI, no differences were reported between patients who developed BSI compared to those who did not. This may be due to the low number of patients in our study or to the fact that source control in those patients with BSI, mostly catheter-related, was usually easily performed within <48 h from diagnosis.

Lastly, we evaluate patient and graft survival according to preservation modality, showing no significant differences. Again, this finding supports HOPE as an effective and safe procedure in the setting of LT, leading to an increased number of eligible organs for transplant without any detrimental impact on patient or graft survival.

In contrast with the data from the Groningen group (27), our study shows that, although not significantly different from that related to SCS, the risk of donor-recipient microbial transmission in recipients of HOPE-treated grafts is low. Considering this minimal risk, our data do not justify a systematic change of antimicrobial prophylaxis when using HOPE.

Our study has several limitations. First, this was a single-center study and microbiological data may be affected by local epidemiology. Second, HOPE perfusate samples were not routinely sent for microbiological examination; however, obtain a sample of HOPE perfusate, ideally at the end of machine perfusion, could be considered to gather more information on potential contaminants in case the recipient presents with signs of infection during the postoperative period. Lastly, by study design we evaluated only infections presenting within 10 days from LT, i.e., those more likely due to donor-recipient transmission, potentially missing donor-related infections with delayed clinical presentation. Its strengths are the study design selecting a cohort of low-risk patients and accounting for potential confounders, and the large sample size.

Conclusions

In conclusion, our results show no difference in the risk of clinically relevant infection, donor-derived infection, and positivity of PFs in LT performed using HOPE *vs.* SCS. Patient survival and grafts survival were shown to be similar as well. These results confirm the safety of HOPE use in LT and corroborate its potential in increasing donor yield without detrimental consequences for recipients.

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Footnote

Reporting Checklist: The authors have completed the STROCSS reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-552/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted according to the principles of the Declaration of Helsinki and its subsequent amendments and the Declaration of Istanbul and was approved by the Institutional Ethics Committee of the City of Health and Sciences of Turin (CET resolution nr. 506/2021). Informed

consent was waived because of the retrospective nature of the study and the fact that the analysis used anonymous clinical data.

References

1. Bodzin AS, Baker TB. Liver Transplantation Today: Where We Are Now and Where We Are Going. Liver Transpl 2018;24:1470-5.
2. Schilsky ML, Moini M. Advances in liver transplantation allocation systems. World J Gastroenterol 2016;22:2922-30.
3. De Carlis R, Paolo Muiesan, Taner B. Donation after circulatory death: Novel strategies to improve the liver transplant outcome. J Hepatol 2023;78:1169-80.
4. Sousa Da Silva RX, Weber A, Dutkowski P, et al. Machine perfusion in liver transplantation. Hepatology 2022;76:1531-49.
5. Ivanics T, Abreu P, De Martin E, et al. Changing Trends in Liver Transplantation: Challenges and Solutions. Transplantation 2021;105:743-56.
6. Foley DP. Comparing preservation solutions for static cold storage in donation after circulatory death liver transplantation. Liver Transpl 2022;28:1423-4.
7. van Rijn R, Schurink IJ, de Vries Y, et al. Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. N Engl J Med 2021;384:1391-401.
8. Schlegel A, de Rougemont O, Graf R, et al. Protective mechanisms of end-ischemic cold machine perfusion in DCD liver grafts. J Hepatol 2013;58:278-86.
9. Schlegel A, Graf R, Clavien PA, et al. Hypothermic oxygenated perfusion (HOPE) protects from biliary injury in a rodent model of DCD liver transplantation. J Hepatol 2013;59:984-91.
10. Patrono D, Cussa D, Sciannameo V, et al. Outcome of liver transplantation with grafts from brain-dead donors treated with dual hypothermic oxygenated machine perfusion, with particular reference to elderly donors. Am J Transplant 2022;22:1382-95.
11. Patrono D, Surra A, Catalano G, et al. Hypothermic Oxygenated Machine Perfusion of Liver Grafts from Brain-Dead Donors. Sci Rep 2019;9:9337.
12. Czigany Z, Uluk D, Pavicevic S, et al. Improved outcomes after hypothermic oxygenated machine perfusion in liver transplantation-Long-term follow-up of a multicenter randomized controlled trial. Hepatol Commun 2024;8:e0376.
13. Panayotova GG, Lunsford KE, Quillin RC 3rd, et al. Portable hypothermic oxygenated machine perfusion for organ preservation in liver transplantation: A randomized, open-label, clinical trial. Hepatology 2024;79:1033-47.
14. Tingle SJ, Dobbins JJ, Thompson ER, et al. Machine perfusion in liver transplantation. Cochrane Database Syst Rev 2023;9:CD014685.
15. Grąt M, Ligocka J, Lewandowski Z, et al. Incidence, pattern and clinical relevance of microbial contamination of preservation fluid in liver transplantation. Ann Transplant 2012;17:20-8.
16. Schlegel A, Mueller M, Muller X, et al. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol 2023;78:783-93.
17. Parente A, Tirotta F, Pini A, et al. Machine perfusion techniques for liver transplantation - A meta-analysis of the first seven randomized-controlled trials. J Hepatol 2023;79:1201-13.
18. Levi Sandri GB, Meniconi RL, Colasanti M, et al. Continuous monitoring of the liver graft temperature: relationship between bacterial contamination of the perfusion fluid and early outcome. Ann Transl Med 2016;4:397.
19. Ruiz P, Gastaca M, Gonzalez J, et al. Incidence and clinical relevance of bacterial contamination in preservation solution for liver transplantation. Transplant Proc 2009;41:2169-71.
20. Reimondez S, Chamorro ML, Alcaraz Á, et al. Preservation fluid cultures. Clinical significance in liver transplantation. Medicina (B Aires) 2021;81:555-8.
21. Oriol I, Lladó L, Vila M, et al. The Etiology, Incidence, and Impact of Preservation Fluid Contamination during Liver Transplantation. PLoS One 2016;11:e0160701.
22. Oriol I, Sabé N, Tebé C, et al. Clinical impact of culture-positive preservation fluid on solid organ transplantation: A systematic review and meta-analysis. Transplant Rev (Orlando) 2018;32:85-91.
23. Audet M, Piardi T, Panaro F, et al. Incidence and clinical

significance of bacterial and fungal contamination of the preservation solution in liver transplantation. Transpl Infect Dis 2011;13:84-8.
24. Chaim FH, Boin IF, Ataide EC, et al. Perfusion fluid contamination in relation to recipient survival and acute cellular rejection in orthotopic liver transplantation: retrospective analysis. Transplant Proc 2011;43:1313-5.
25. Oriol I, Sabe N, Càmara J, et al. The Impact of Culturing the Organ Preservation Fluid on Solid Organ Transplantation: A Prospective Multicenter Cohort Study. Open Forum Infect Dis 2019;6:ofz180.
26. Lau NS, Ly M, Dennis C, et al. Microbial Contamination During Long-term Ex Vivo Normothermic Machine Perfusion of Human Livers. Transplantation 2024;108:198-203.
27. Endo C, Lascaris B, Brüggenwirth IMA, et al. The Risk of Microbial Transmission in Recipients of Donor Livers That Underwent Hypothermic or Normothermic Machine Perfusion. Transplant Direct 2024;10:e1664.
28. Viero G, Lombardi A, Antonelli B. Hypothermic oxygenated machine-perfusion fluid-related infection in a liver transplant recipient: First case report in the literature. Transpl Infect Dis 2023;25:e14056.
29. Patrono D, Zanierato M, Vergano M, et al. Normothermic Regional Perfusion and Hypothermic Oxygenated Machine Perfusion for Livers Donated After Controlled Circulatory Death With Prolonged Warm Ischemia Time: A Matched Comparison With Livers From Brain-Dead Donors. Transpl Int 2022;35:10390.
30. Ghinolfi D, Patrono D, De Carlis R, et al. Liver transplantation with uncontrolled versus controlled DCD donors using normothermic regional perfusion and ex-situ machine perfusion. Liver Transpl 2024;30:46-60.
31. Lavezzo B, Patrono D, Tandoi F, et al. A simplified regimen of targeted antifungal prophylaxis in liver transplant recipients: A single-center experience. Transpl Infect Dis 2018;20:e12859.
32. EUCAST. Clinical breakpoints and dosing of antibiotics. (Cited 2024 Sep 13). Available online: https://www.eucast.org/clinical_breakpoints
33. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
34. National Healthcare Safety Network. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). 2024. Available online: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf
35. CDC. Infection Control. Catheter-Associated Urinary Tract Infections (CAUTI) Prevention Guideline. 2024. (Cited 2024 Aug 30). Available online: https://www.cdc.gov/infection-control/hcp/cauti/index.html
36. NICE. Pneumonia in adults: diagnosis and management. 2014. (Cited 2024 Aug 30). Available online: https://www.nice.org.uk/guidance/cg191
37. Sartelli M, Coccolini F, Kluger Y, et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg 2021;16:49.
38. Echenique IA, Ison MG. Update on donor-derived infections in liver transplantation. Liver Transpl 2013;19:575-85.
39. Dolci G, Burastero GJ, Paglia F, et al. Epidemiology and Prevention of Early Infections by Multi-Drug-Resistant Organisms in Adults Undergoing Liver Transplant: A Narrative Review. Microorganisms 2023;11:1606.
40. Shbaklo N, Tandoi F, Lupia T, et al. Bacterial and Viral Infections in Liver Transplantation: New Insights from Clinical and Surgical Perspectives. Biomedicines 2022;10:1561.
41. Wolfe CR, Ison MG; AST Infectious Diseases Community of Practice. Donor-derived infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13547.
42. Attia M, Silva MA, Mirza DF. The marginal liver donor--an update. Transpl Int 2008;21:713-24.
43. Neil DAH, Minervini M, Smith ML, et al. Banff consensus recommendations for steatosis assessment in donor livers. Hepatology 2022;75:1014-25.
44. Aggarwal S, Kang Y, Freeman JA, et al. Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. Transplant Proc 1987;19:54-5.
45. Hilmi I, Horton CN, Planinsic RM, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. Liver Transpl 2008;14:504-8.
46. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943-9.
47. Agopian VG, Harlander-Locke MP, Markovic D, et al. Evaluation of Early Allograft Function Using the Liver Graft Assessment Following Transplantation Risk Score Model. JAMA Surg 2018;153:436-44.
48. Dindo D, Demartines N, Clavien PA. Classification of

surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
49. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1-7.
50. Eden J, Brüggenwirth IMA, Berlakovich G, et al. Long-term outcomes after hypothermic oxygenated machine perfusion and transplantation of 1,202 donor livers in a real-world setting (HOPE-REAL study). J Hepatol 2025;82:97-106.
51. Hann A, Lembach H, Dassanayake B, et al. Severe Sepsis Mimicking Primary Nonfunction Following Liver Transplantation: Normothermic Machine Perfusion Is a Potential Environment for Bacterial Overgrowth and Transmission From Donor to Recipient. A Case Report. Transplant Proc 2020;52:2781-5.
52. Qureshi S, Elliott H, Noel A, et al. Infection and Prophylaxis During Normothermic Liver Perfusion: Audit of Incidence and Pharmacokinetics of Antimicrobial Therapy. Transplantation 2024;108:1376-82.
53. Sidhu SK, Malhotra S, Devi P, et al. Significance of coagulase negative Staphylococcus from blood cultures: persisting problems and partial progress in resource constrained settings. Iran J Microbiol 2016;8:366-71.

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