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REVIEW

The economic impact of machine perfusion technology in liver transplantation

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Abstract

Introduction: Several clinical studies have demonstrated the safety, feasibility, and efficacy of machine perfusion in liver transplantation, although its economic outcomes are still underexplored. This review aimed to examine the costs related to machine perfusion and its associated outcomes.

Methods: Expert opinion of several groups representing different machine perfusion modalities. Critical analysis of the published literature reporting the economic outcomes of the most used techniques of machine perfusion in liver transplantation (normothermic and hypothermic ex situ machine perfusion and in situ normothermic regional perfusion).

Results: Machine perfusion costs include disposable components of the perfusion device, perfusate components, personnel and facility fees, and depreciation of the perfusion device or device lease fee. The limited current literature suggests that although this upfront cost varies between perfusion modalities, its use is highly likely to be cost-effective. Optimization of the donor liver utilization rate, local conditions of transplant programs (long waiting list times and higher MELD scores), a decreased rate of complications, changes in logistics, and length of hospital stay are potential cost savings points that must highlight the expected benefits of this intervention. An additional unaccounted factor is that machine perfusion optimizing donor organ utilization allows patients to be transplanted earlier, avoiding clinical deterioration while on the waiting list and the costs associated with hospital admissions and other required procedures.

Conclusion: So far, the clinical benefits have guided machine perfusion implementation in liver transplantation. Albeit there is data suggesting the economic benefit of the technique, further investigation of its costs to healthcare systems and society and associated outcomes is needed.

KEYWORDS

cost-analysis, health economics, hypothermic machine perfusion, liver transplantation, machine perfusion of the liver, normothermic machine perfusion, normothermic regional perfusion

1 | INTRODUCTION

Since the 1980s, little progress has been made in liver graft preservation until the development of machine perfusion technology.[1] Machine perfusion of the liver (MPL) is currently a hot topic in liver transplantation because it allows oxygenated preservation and/or resuscitation of the donor organ, thereby mitigating ischemia-reperfusion injury (IRI).[2] This aspect is crucial when considering organ transplantation from high-risk donors, the so-called extended criteria donors (ECD). Those organs are more vulnerable to IRI and, thus, associated with poor post-transplant function and decreased graft survival rates after liver transplantation.[2,3] MPL can be applied in situ, during donation after circulatory death (DCD) donor organ recovery (normothermic regional perfusion), or ex situ, after the recovery of the organ. Ex situ MPL can be performed at different temperatures (hypothermic, subnormothermic, and normothermic) and timings (preservation approach, perfusion starts at the donor hospital; or, in an end-ischemic approach, wherein perfusion will begin after arrival of the donor organ at the recipient hospital).[3,4]

The safety, feasibility, and efficacy of MPL have been demonstrated for several indications and techniques.[5] Two randomized clinical trials (RCT) applying normothermic machine perfusion (NMP) of the liver to regular and ECD organs confirmed its safety and efficacy.[6,7] The same was verified for hypothermic machine perfusion (HMP) in two recently published RCTs.[8,9]

Although the need to safely increase ECD organ utilization renewed interest in MPL, clinical safety/efficacy is currently driving economic outcomes. Clinical outcomes are indeed fundamental in health technology assessment, albeit it requires careful consideration also of economic aspects. Therefore, it is now time to analyze the costs of the therapy to healthcare systems and society. This review article aimed to examine the existing literature on this subject and compare the costs related to the most used techniques of MPL and the outcomes associated with these options.

2 | EX SITU NORMOTHERMIC MACHINE PERFUSION OF THE LIVER

The capacity of NMP to offer a near-physiological environment to donor organs allows the re-establishment of its full metabolism, although the impact of their physiological interaction with other organs and metabolites is not known thus far.[10] A fully active organ must be able to perform its metabolic functions adequately, if not severely and irreversibly injured. This concept supports the ability of NMP to evaluate the viability of donor organs prior to transplantation.[10] In addition to assessing donor organ function, it is also possible to measure hepatocellular and bile duct injury biomarkers throughout perfusion.[10–12] Although definitive viability criteria are still not defined—probably must prove to be organ-specific in future—and critics claim reperfusion on the device may be detrimental to the organ, the verification of functioning is reassuring for transplant surgeons and favors donor organ utilization.[6,11] Besides, most likely, a fully active organ would be ideal for ex situ therapeutic interventions.[13]

Nasralla et al. in an RCT[6] demonstrated preservation with NMP has the potential to reduce the donor organ discard rate, even though criticisms exist regarding randomization before final organ acceptance when comparing clinical outcomes—which may have introduced selection bias.[14–16] The beneficial impact of end-ischemic NMP on donor organ utilization was later highlighted by the VITTAL clinical trial (clinicalTrials.gov number NCT02740608), performed by the Birmingham group.[17] In this prospective, non-randomized, phase 2 trial, viability assessment with NMP allowed transplantation of 71% of discarded livers that were perfused with the intent of transplantation, with 100% 90-day patient and graft survival.[17] Raigani et al. more recently used the same NMP criteria to assess the viability rate of 21 discarded human donor livers, and 55% of the livers perfused were considered transplantable.[18] Extrapolating this rate to a matched cohort (by the donor risk index) of discarded donor livers in the United States, authors expected potentially 398 additional transplants annually.[18] Additionally, the DHOPE-COR-NMP trial from Groningen demonstrated the safety and feasibility of transplantation of initially declined high-risk donor livers after viability assessment, which led to a 20% increase in the number of deceased donor livers in their center.[19]

In the first cost-analysis of end-ischemic NMP, Raigani et al. reported that the median cost to perform NMP was US$15 454.[18] In order to calculate these figures, direct (perfusion device disposable, perfusate components, and point-of-care equipment) and indirect (personnel and facility fees, and depreciation of the perfusion device) costs were considered. At a 55% viability rate, the median cost to find a transplantable liver was US$28 099, just slightly more than the estimated monthly Medicare expenses of US$22 685 for the care of a patient with a model for end-stage liver disease (MELD) 30.[18] They conclude that the expected benefits of NMP will be more apparent if efforts to enhance the viability rate are adopted and if this technology is applied in areas with long waiting list times and higher MELD scores.[18] Notably, pharmacological interventions during NMP are suggested as a possible approach

to increase the recovery of steatotic organs and a combination of perfusion modalities may also play a role for ischemically injured donor organs.[19–21]

Recently, a cost-effectiveness evaluation was performed encompassing the results of the first RCT on liver transplantation with NMP and national standard sources in the United Kingdom.[6,22] A de novo decision-analytic model was developed to estimate the costs and outcomes in each strategy over a lifetime time horizon. Additional costs related to the OrganOx device were the costs of disposables and solutions (£6000 [US$8160]), staff costs (£500 [US$680]), and a device lease fee of £30 000 (US$40 800) per year per hospital.[22] Costs of follow-up care, immunosuppressants, and visits to specialists and general doctors for follow-up after transplantation were also considered. Liver transplantation using the OrganOx metra for NMP was more costly (£46 711 [US$63 527] vs. £37 370 [US$50 823]) and more effective (10.27 QALYs vs. 9.09 QALYs) than SCS preserved organs.[22] The study concluded that using the device in an ex-situ preservation approach is highly likely to be cost-effective (at a £20 000 [US$27 200] willingness-to-pay threshold).[22]

An introductory article to an ongoing detailed Canadian cost-effectiveness study investigating NMP (with OrganOx metra™, OrganOx Limited, Oxford, United Kingdom) and liver transplantation anticipated this technique could potentially reduce costs by changing logistics at the hospital.[23] While authors acknowledged OrganOx cost per run is considerable (Can$18 593.02 [US$15 060.35]–20 241.35 [US$16 395.49]), the possibility to cut night-time extra-salary, as well as the rate of complications and length of hospital stay, are potential cost savings points of intervention.[23] However, this aspect is highly dependent on the setting of each hospital, and this may compromise its generalization. This is because moving transplant cases to regular hours may cause cancellation of elective procedures and decrease revenues since most operating theatres operate at maximum capacity during those hours. In addition, payment of extra salary for night cases is not a routine globally.

The same group recently published the results of cost-utility analysis of a single-center retrospective study comparing NMP and SCS in Canada.[24] The mean cost of transplant for NMP was US$456 455, and SCS was US$519 222. NMP leads to greater incremental QALYs gains over 5 years (3.48 vs. 3.17, respectively). They reported that using NMP (with OrganOx metra) in a transplant program is cost-effective and likely to be cost-saving for healthcare systems, compared to SCS. In addition, NMP was associated with a higher number of lives saved and decreased waitlist figures and mortality rate.[24] The authors concluded that implementation of NMP in a liver transplant program results in greater QALY gains and is cost-effective from the public healthcare payer perspective.[24]

The real economic impact of NMP in some approaches is technically challenging to quantify in certain aspects. For example, suppose the NMP is utilized to deliver the standard day-to-day transplants with direct comparison of costs of organ preservation and subsequent transplant plus the outcomes until a patient is recovered from the operation. In that case, there seems to be an added extra cost—owing to both reusable and non-reusable equipment costs. The question remains, why the NMP is required when it is proven for over half a century the success of liver transplantation practice. It is unlikely that many transplant centers embracing the technology perform NMP in the routine transplant practice; thus, direct comparisons are not feasible. Most of the centers would transplant marginal grafts which would otherwise be discarded or not considered for transplantation with the help of NMP, which would inherently be associated with early allograft dysfunction, increased supportive care in the intensive care unit, etc Therefore, if a study is designed only to assess the cost-benefit analysis, the primary aim must be the economic benefits, and the study should be powered accordingly. Unfortunately, most of the trials that have been published thus far and the ones in the pipeline have not and will not address this issue. The main goal of the clinicians and researchers is to focus on clinical benefits rather than financial benefits. Therefore, the available cost analysis is extrapolating on most occasions, and there is potential that some of the costs related to the manpower of initiating and maintaining NMP liver graft in physiological conditions until the transplant operation is carried out are largely unaccounted. Compared to SCS, NMP requires expert surgical skills in the initiating and trouble-shooting phase and this period may last up to 2–4 h in most scenarios. A senior consultant in the decision-making is necessary for the procedure until a skilled staff is trained, and this factor is discounted in most of the cost analysis.

One area that has not been completely studied is the overall healthcare benefits of the transplant service as a whole and or a particular healthcare institution by employing the NMP program. In Birmingham in the United Kingdom, a novel service delivery protocol was established to benefit surgically complex and sicker patients to be transplanted with so-called orphan livers.[25] This project mainly focused on transplanting those patients following a previous transplant due to graft failure for various reasons, many of them are sicker and treated as "in-patients". Generally, 10% to 15% of wait-listed patients in any transplant program are candidates to re-transplantation due to late vascular, biliary, and disease recurrence indications. Most of these patients suffer recurrent infections and require high-cost antibiotics, do

undergo both non-invasive and invasive procedures, and add burden to bed capacity in both ward and intensive care unit settings. For these patients, the recurrent costs whilst awaiting a re-transplant could only be stopped or minimized by carrying out a repeat transplant procedure at the earliest possible opportunity. An early cost analysis study in this setting showed that patients transplanted gained 16.5 QALY with £3763 (US$5118)/per QALY. Cost per QALY in patients <34 years is £3083 (US$4193) compared to £4520 (US$6147) in patients >65 years.[26] Despite the complex transplant procedure, the postoperative management costs did not increase, and probably the costs incurred NMP. In addition to the overall costs of patient care, this helps in the overall economic impact of patient movement through an organization; therefore, the benefits are many-fold.

A comprehensive understanding of the mainstream of NMP utilization is crucial when planning to perform health economic outcomes research. More consistently, the existing literature suggests NMP has the potential for optimization of donor organ utilization, which may likely increase the number of transplants performed.[6,18] Consequently, patients should be transplanted earlier, avoiding clinical deterioration during the waiting list and the costs associated with hospital admissions and other required procedures. However, data demonstrating this later benefit are still missing. In addition, although there is a suggested logistic benefit to hospitals because NMP allows a prolongation of preservation time,[23] moving transplantation to daytime, and reducing staffing costs, the impact of this economic benefit depends on the local billing set up for transplantation.

3 | IN SITU NORMOTHERMIC REGIONAL PERFUSION

In situ normothermic regional perfusion (NRP) is a machine perfusion strategy applied in DCD to restore the flow of oxygenated blood to a region of circulation (abdomen [A-NRP] or thorax and abdomen [TA-NRP]) following the donor warm ischemic period and declaration of death, without an intervening period of hypothermia.[27] Reperfusion performed in this manner has been seen to effectively restore depleted energy substrates, remove metabolic waste products, and induce antioxidant and other endogenous protective mechanisms against IRI prior to cold preservation and recovery.[28–31] As of this writing, clinical experience with TA-NRP, which is more complex than A-NRP, remains anecdotal. Similarly, uncontrolled DCD (uDCD) is more complicated than controlled DCD (cDCD), performed at very few hospitals in the world, and universally performed with postmortem NRP, making cost comparisons in the uDCD context meaningless. For these reasons, the remainder of this section will focus on A-NRP in cDCD.

The European Society of Organ Transplantation (ESOT) recently organized an international group of experts to identify basic technical requirements for performing postmortem NRP in DCD.[32] As a result, the following minimum requirements were described: (1) Team: At least two surgeons (may be replaced by intensivists or interventional radiologists in some settings), scrub nurse, circulating nurse, and perfusionist; (2) Circuit: Pump and heat exchanger (reusable circuit components), connected via a pre-manufactured disposable kit, including tubing, membrane oxygenator, and pump head, donor via an arterial and venous cannula (disposable circuit components); (3) Priming solution: Enough crystalloid solution to fill cannula and circuit tubing; (4) Mandatory adjuncts: Packed red blood cells to maintain hemoglobin >8–10 g/dl and heparin to maintain activated clotting time in the therapeutic range; (5) Discretionary adjuncts: Cannula insertion kits (including needles for vessel localization and guidewires or small-bore catheters for vessel access), antimicrobial drug(s), bicarbonate, mannitol, and steroids.

Based on these additional expenditures, the cost of the cDCD procedure increases by €2500 (US$2900)-€5000 (US$5800) in Spain with respect to donation after the neurologic determination of death and to cDCD performed with the standard rapid recovery (SRR) technique (lower end of this range when device and personnel are "in house," higher-end when they have to be transported from another center).[33] In other countries, per-procedure costs for NRP range from approximately €3500 (US$4060) in Belgium to €1800 (US$2088) in France, €2500 (US$2900) in Italy, and £2900 (US$3944) in the United Kingdom.

While at present ex situ machine perfusion treats a single organ, in situ NRP offers the ability to treat up to four transplantable organs in the abdomen (two kidneys, liver, pancreas—as of this writing, use of small bowel from cDCD donors recovered with NRP has not been reported). To date, the impact of in situ NRP has not been evaluated in the context of a RCT. This is due, in part, to the compulsory nature of NRP application in DCD in several European countries (France, Italy, Norway)[34]; increasing preference for NRP in countries where different options for cDCD recovery are permitted (e.g., Spain)[33]; and above all difficulty in identifying an adequate trial design. In situ NRP is applied in the DCD donor immediately following declaration of death and prior to organ assessment what makes organ utilization analysis difficult to be compared with other methods. An RCT comparing NRP with the alternative—SRR—would require randomizing donors and, consequentially, organs at a point when none have

been accepted. As such, any RCT on NRP is inherently at risk for selection bias. It is impossible to blind donor surgeons to the recovery method and highly probable that disparate numbers of organs would be accepted, and donor profiles would vary significantly according to the recovery method used. Donor surgeons might be more inclined to accept organs with a "riskier" profile recovered with NRP, for example, as NRP allows for some pre-recovery viability assessment not offered by SRR. Alternatively, the option of comparing in situ NRP with ex situ MPL in the liver still does not ensure the absence of selection bias; does not adequately address the risk to and potential loss of "bystander" organs (kidneys, pancreas).[35,36]

While most must agree that having an RCT to assess the value of NRP is desirable, also they must admit that their development is challenging. Randomization between NRP or SRR only after donor offer acceptance for a specific patient may mitigate to some extent the donor selection bias and eliminate potential recipient selection bias; albeit donor assessment must be done prior to the declaration of death—which may limit the sample to controlled DCD. The selection of primary outcomes for such RCT must consider the risk of bias if donor organ utilization is evaluated, therefore, test for clinical outcomes may be a more reasonable option. In addition, although blinding surgeons to the recovery method is unfeasible, recipients and the independent assessment committee may be blinded.

Data supporting the use of NRP in cDCD is provided by observational studies, primarily arising from Europe. A recent systematic review and meta-analysis determined the use of postmortem NRP in cDCD liver transplantation was associated with a 71% reduction in the development of any form of biliary stricture(s) (relative risk [RR] 0.29, 95% confidence interval [CI] 0.15–0.57) and 85% reduction in ischemic-type biliary lesions (ITBL) (RR 0.15, 95% CI 0.105–0.45) relative to SRR.[37] Decreased risk of liver graft loss (adjusted hazard ratio [HR] 0.39, 95% CI 0.20–0.78) has also been described in the context of a propensity-adjusted multicenter study.[38] For cDCD kidneys, the use of postmortem NRP has been seen to lead to a 49% reduction in delayed graft function (odds ratio [OR] 0.51, 95% CI 0.37–0.70) and 44% reduction in one-year graft loss (OR 0.56, 95% CI 0.32–0.99) in a propensity-matched multicenter study comparing NRP and SRR.[39] While few reports on cDCD pancreas transplants performed with postmortem NRP have been published, excellent (100%) one-year graft survival has been described.[40]

In Spain in 2019, 678 and 444 cDCD kidneys were evaluated with NRP and SRR, respectively, and 528 (78%) and 309 (70%), respectively, were transplanted. For cDCD livers, 298 and 75 were evaluated with NRP and SRR, respectively, with 195 (65%) and 29 (39%) being transplanted. As well, 27 cDCD pancreata were evaluated with NRP, while only 4 were assessed with SRR; ultimately, 5 (7%) and 0 pancreata were transplanted from each. In general terms, the use of NRP in cDCD resulted in a nearly 40% increase in organ utilization rates when compared with cDCD performed with SRR.

No cost studies have been published regarding the economic impact of performing NRP in cDCD. While a formal cost analysis is beyond the scope of this review article, we can provide the following brief cost-benefit assessment. Assuming an average of €3000 (US$3480) in additional costs per procedure, a theoretical pool of 100 cDCD donors hypothetically declined for a donation of all organs undergoing NRP would present an additional €300 000 (US$348 000) in upfront costs relative to the same group undergoing SRR. If the use of NRP increases the donor pool by adding organs that would normally be discarded, this upfront cost increase, however, could be offset by the following:

- Removing 16 additional patients from hemodialysis (>€47 000 [US$54 520] per year in Spain to care for a patient with end-stage renal failure on hemodialysis).[41]
- Avoiding delayed graft function and post-transplant hemodialysis in 20 cDCD kidney recipients (approximately €1000 [US$1160] for a week of hemodialysis).[39,41]
- Removing 26 additional patients from the liver transplant waiting list (approximately €2300 [US$2668] and €8600 [US$9976] per patient per year to care for decompensated cirrhosis and hepatocellular carcinoma, respectively).[42]
- Avoiding biliary complications in at least 23 cDCD liver recipients, including at least 11 cases of ITBL (approximately €5700 [US$ 6612] for endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography admission and €11 800 [US$13 688] for surgical hepaticojejunostomy).[43]
- Curing 7 additional patients of (type I) diabetes mellitus (at least €3000 [US$3480] for a year of care).[43]
- Losing 4 fewer kidney grafts and at least 12 fewer liver grafts by the end of the first post-transplant year.[38,39]

While these figures are rough, unadjusted estimates and do not account for important differences in patients' quality of life offered by transplantation relative to continuing in a state of organ failure, they speak for the first time to some of the potential clinical and economic benefits offered by applying postmortem NRP in cDCD. First, however, it would be necessary to test NRP clinical and economic benefits in a randomized trial.

4 | EX SITU HYPOTHERMIC OXYGENATED MACHINE PERFUSION OF THE LIVER

While dynamic preservation by machine perfusion at normothermic temperatures creates a near-physiological environment in which the liver is fully metabolically active, hypothermic oxygenated machine perfusion (HOPE) reduces the graft's metabolism to around 10% of normothermia.[4] End-ischaemic HOPE is a relatively simple, yet effective approach if it comes to reducing IRI-related complications. Donor livers are transported using SCS and subjected to MPL after the arrival at the recipient center in an end-ischemic approach or as a preservation method from donor hospital up to transplantation. Two hours of end-ischemic HOPE is sufficient to restore mitochondrial function prior to reperfusion of the liver and minimize IRI.[44] Recently, the results of the first international multicenter RCT (DHOPE-DCD trial) comparing dual HOPE versus SCS were published.[8] Recipients of dual HOPE-perfused DCD livers had a 68% reduction in risk of clinically relevant non-anastomotic biliary strictures at 6 months after liver transplantation compared to recipients of non-perfused DCD grafts. In addition, the risks of developing the post-reperfusion syndrome and early allograft dysfunction were reduced by 57% and 39%, respectively, in the machine perfusion group.[8]

Since the metabolism of the donor liver is limited during HOPE, the organ produces fewer waste products compared to NMP, thereby reducing the need to make adjustments to the perfusate during perfusion and minimizing labor. From Groningen's experience, the minimum personnel required for an end-ischemic HOPE procedure would be one surgeon and a trained organ perfusionist. After connecting the liver to the machine by the surgeon, the perfusion only requires monitoring of the liver graft by the organ perfusionist. The most commonly used perfusion solution for HOPE (i.e., University of Wisconsin machine perfusion solution) costs around US$400 per liter, which is, in most countries, less compared to human blood products or other solutions with an oxygen carrier. Approximately 4 liters of machine perfusion solution are required to allow dynamic HOPE preservation, including flushing the graft prior to connection. No further perfusion additives, such as electrolytes, antibiotics, nutrients, or albumin, are needed during HOPE. Taking into account perfusate composition, personnel, and perfusion duration, the costs for HOPE are likely to be much less, compared to NMP, but no direct comparison has yet been made.

Only one cost-effectiveness study has been published evaluating the financial impact of end-ischemic HOPE from a hospital perspective. In a sub-analysis of the PERPHO trial from France, costs and revenue for end-ischemic HOPE versus SCS were analyzed for recipients of livers donated after brain death (DBD).[45] For each recipient in the trial, hospital stay costs in either group were calculated. For the HOPE group, specifically, costs of amortization of the machine, disposable kits, perfusion solution, and machine maintenance were included. Total costs for the machine perfusion device, including maintenance, were estimated at €765 (US$913) per patient according to an amortization time of 7 years with 25 procedures per year. Costs for the disposable kits and perfusion solution were estimated at €4195 (US$5007) and €338 (US$403) per patient, respectively. Therefore, total additional costs for end-ischemic HOPE were estimated at €5298 (US$6323) per patient. However, this does not include the costs for an organ perfusionist. Reduced hospital length of stay and fewer postoperative complications in the HOPE group compensated for the additional material costs. Therefore, the average difference between cost and revenue was similar between the HOPE and SCS group (€3023 [US$3583] vs. €4059 [US$4811], respectively). In the DHOPE-DCD trial, hospital length of stay was not reduced in the dual HOPE group, but the number of readmissions and biliary interventions within 6 months after the transplant were fourfold lower. During the first 6 months after liver transplantation, 5 of 78 patients in the dual HOPE group required a biliary intervention, and 6 patients were readmitted, whereas 22 of 78 in the SCS group required a biliary intervention, and 17 patients were readmitted. For de DHOPE-DCD trial, a formal, per protocol pre-specified cost-effectiveness assessment is under current investigation.[45]

The recently published German multicenter randomized HOPE-ECD-DBD trial demonstrates that HOPE significantly reduced early allograft injury (peak alanine aminotransferase levels) and improved post-transplant outcomes (90-day complication rate, ICU stay, and hospital stay) in ECD-DBD liver transplantation when compared to SCS.[9] The authors reported that although the costs of a MPL are substantial (approximately €5000 [US$5800] running costs per case), the overall procedural costs reduced by 25% over the first three months in the HOPE group compared to SCS (€13 000 [US$15 080] lower, $P = .016$).[9]

Health-economic evaluations of HOPE versus SCS based on RCTs, such as de DHOPE-DCD trial,[46] and the HOPE trial (clinicaltrials.gov: NCT01317342) will be necessary to consolidate the evidence that improved patient outcomes compensate for higher healthcare costs. Such studies will help to underpin policy decisions regarding reimbursement of machine perfusion procedures. For example, in the Netherlands, end-ischemic HOPE has been accepted as the standard of care for DCD grafts based on the results of the DHOPE-DCD trial, which implies reimbursement.[47] Solid evidence of

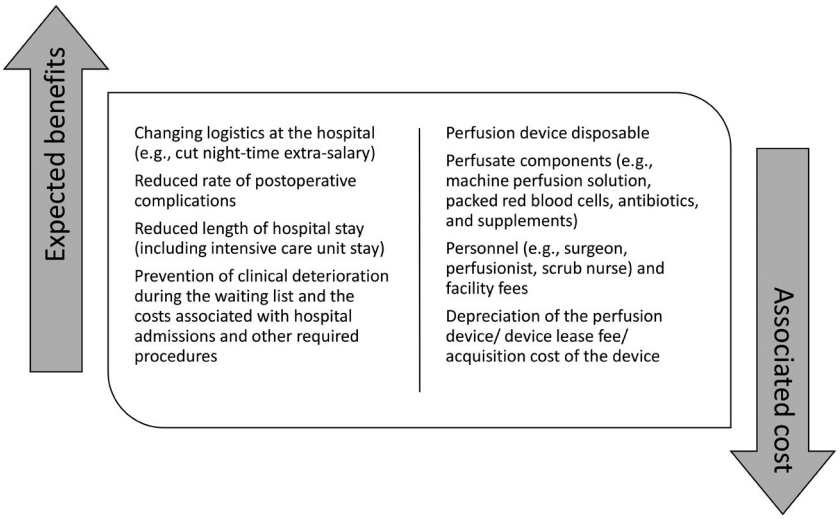

FIGURE 1 Expected benefits and associated cost of machine perfusion in liver transplantation. Currently, there is a suggested health economic benefit related to the use of machine perfusion of the liver endorsed by the improved patient outcome. However, a more consistent indication of its relation to the higher healthcare costs must consider its expected benefits and associated costs

cost-effectiveness for well-defined indications will be essential to allow widespread implementation of end-ischemic HOPE for liver grafts.

5 | DISCUSSION

Healthcare costs play a crucial role in how we practice medicine. The cost of healthcare has increased exponentially over the years and more recently because of the complexity of care and increase in age and disease burden. Improvements in inpatient outcomes may be coming at unsustainable increases in cost.[48] Consequently, clinical and economic advantageous evidence must drive the implementation of new technologies in medicine. The health technology assessment process is moving toward a multidisciplinary approach wherein its safety and efficacy are considered together with economic, ethical, and organizational aspects.[49]

Cost-analysis studies on MPL are currently starting to emerge to attend to a perceived demand in the field.[18,22,45] Thus far, the clinical benefits have driven the implementation of MPL programs; nevertheless, liver transplant professionals increasingly realize that full implementation of these programs passes through administrative hospital staff and local health authorities. Financial constraints force these professionals to make hard choices and evaluate the return on investment of health interventions more critically than ever. Thus, in addition to altruistic reasons, economic arguments are needed to assure them about the need to adopt this new technology.

Some measures are already suggested to counterbalance the additional costs related to the device, disposable, solutions, staff costs, and underline the benefits of MPL. For example, the establishment of measures to enhance the viability rate of ECD-organs, and MPL utilization preferentially within scenarios of long waiting list times and higher MELD scores.[18] Furthermore, it can change logistics at the hospital and even cut night-time extra-salary, advantages highly dependent on the setting of the transplant unit because it may decrease hospital revenue by canceling elective cases.[23] Finally, MPL might also find potential cost savings points at a reduced rate of postoperative complications and length of hospital stay.[23,45] A so far underexplored benefit of this technique is the possibility of abbreviating patients' waiting list time via optimization of donor organ utilization and increased number of transplants performed. Thereby, MPL must prevent clinical deterioration while on the waiting list and reduce the costs associated with hospital admissions and other required procedures. Figure 1 summarizes the associated costs and expected benefits of machine perfusion in liver transplantation.

Nowadays, the competing demand for funds and limited public budgets drive healthcare professionals to possess economic evaluation skills. Health economic outcomes research or pharmacoeconomic ultimately aim to analyze the total costs of treatment options and the outcomes associated with these options.[50] While models of pharmacoeconomic analysis monetize the input, the method to assess the outcomes varies. For example, for cost-benefit analysis, the input and outcomes are measured in monetary terms (i.e., how institutions can best spend their resources to produce economic benefits); for cost-effectiveness analysis, outcomes are computed in natural units (e.g., lives saved); for cost-utility analysis, the outcomes take into account patient preferences or utilities (e.g., QALY).[50,51] Although cost-benefit analysis is crucial to ensure value for money and efficiency of payers' spending, clinicians and researchers in the field understand that the value of intervention goes beyond costs and cutting costs.

Thus far, machine perfusion programs are still largely based on research and/or internal university or hospital

funding. Although the level of funding differs from those for clinical drug trials, partnership or special commercial conditions are frequently negotiated between the industry and the organizations. Partially, this is because despite the interest to facilitate the introduction of the technology, machine perfusion manufacturers are smaller in size and income. Consequently, the role of industry partners on trial design and analysis should be clearly stated, including holders of data and the responsible parties for analysis, as these relationships can potentially impact study validity and interpretation.[52,53]

Clinicians tend to wait for robust scientific evidence, with statistically significant results of the primary outcome, when assessing a more complex technology associated with higher costs.[54] Albeit, undoubtedly, this approach constitutes the correct method to evaluate scientific evidence, study design, trial methodology, and selection of primary outcomes by researchers are influenced by several variables. Thereby, results in a clinical trial must be appreciated in view of the overall likelihood that one treatment represents a better option for patients than the other.[54] This concept applies to MPL trials, wherein the gold standard comparator is SCS. Considering the current evidence discussed herein, which suggests that the higher up-front costs must be evaluated with downstream cost savings, the economic benefit of MPL is more probable than unlikely.

6 | CONCLUSION

Over the last decade, MPL has gathered momentum due to the need to expand ECD transplantation. A growing body of evidence supports the improved post-transplant outcomes associated with organ preservation and reconditioning applying this device. However, the continuity of the expansion of MPL programs is partly dependent on constructing a solid economic argument. Whilst promising data suggests a favorable cost analysis for MPL utilization, the existing literature on this subject is scarce. Although costs are currently high, increased competition from manufacturers and wider dissemination of the technology could drive down costs. Further studies confirming the financial benefit of this therapy to healthcare systems and society are urgently awaited.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Concept/design, Yuri L. Boteon, and Paulo N. Martins; Data interpretation, drafting article, critical revision, and approval of article, all authors.

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