Editorial Commentary

Standardization is needed in reporting risk and outcomes of machine perfusion in liver transplantation

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We congratulate Yamamoto *et al.* on their study "Impact of Portable Normothermic Machine Perfusion for Liver Transplantation from Adult Deceased Donors" (1). The surge of interest in normothermic machine perfusion (NMP) in the United States (US) has generated considerable enthusiasm. The authors present generally exciting results from their single-center analysis of 541 liver transplantations. Among these, 469 were from donors after brain dead (DBD); 58 (12.4%) received NMP and 411 static cold storage (SCS, 87.6%). Seventy-two transplants were from donors after circulatory death (DCD); 52 (72.2%) received NMP (device-to-donor) *vs.* 20 SCS (27.8%). This retrospective study compared outcomes between device-to-donor NMP and traditional SCS, stratifying for donor type to account for different risk profiles. Both DBD and DCD liver recipients with upfront NMP demonstrated a reduced rate of early allograft dysfunction (EAD) and post-reperfusion syndrome (PRS). Additionally, the authors describe lower ischemic cholangiopathy (IC) rates in DCD grafts when upfront NMP was used. Overall and major biliary complications, such as non-anastomotic biliary strictures (NAS), which Yamamoto *et al.* defined as IC, are highly relevant and often the primary factors limiting the higher utilization of DCD livers. Despite the growing excitement, it is key to delve into "real world" outcomes of NMP in clinical practice to fully understand its implications and optimize its use.

Yamamoto *et al.*'s findings echo previous studies, affirming the potential of NMP, both upfront and back-to-base (i.e., NMP after SCS during transport), to mitigate EAD and improve other 3-month outcomes (2-5). However, we harbor reservations regarding the methodologies employed in this study and propose avenues for future scientific exploration.

Primarily, the study would have benefited from more standardized reporting of results. Yamamoto *et al.* compared 1-, 3- and 5-year outcomes between SCS and upfront NMP approaches, using the TransMedics OCS® system (1). Discrepancies exist in exposure times to post-operative complications between the study groups, with OCS® cases inherently conducted later in the study period. At time of publication, many cases may have conceivably had less than 1 year posttransplant follow-up, as the TransMedics OCS® was not approved for clinical use until late 2021 (6). This temporal imbalance could skew results, notably impacting the NMP cohort. Finally, the sample size in the DCD cohort was quite small, particularly the control cohort (DCD-SCS n=20). Thus, drawing definite

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Table 1 Stated claims and published evidence regarding the impact of NMP

Perfusion approach	Claimed benefit	Actual evidence
Device-to-donor (upfront) NMP	Prevents NAS and ischemic cholangiopathy	Potential reduction in NAS (determined by committee) in standard/low-risk grafts (1,2)
	Allows safe use of riskier grafts	Risk-matched outcomes have not been reported
		No cohort has yet evaluated exclusively outside benchmark criteria
	Improves outcomes of liver transplant	Does reduce EAD, which may improve early complications (1,2). Long-term complications and survival have not been reported
		Likely no difference in graft loss or survival up to 1 year (7)
	Is cost acceptable due to improved complications	Standardized cost analysis has not been reported yet
		Detailed complication analysis in a risk matched cohort is lacking
	Is superior to end-ischemic NMP due to reduction in pre-NMP ischemia time	Two studies have compared end-ischemic and upfront NMP, which showed no difference in low or standard risk grafts within benchmark criteria (8,9)
		The are no other risk-matched comparisons
End-ischemic NMP (back-to-base)	Allows safe use of riskier grafts	Might allow increased use (VITTAL trial), though NAS rates are comparably high as seen with SCS alone in riskier cohorts (10,11)
	Improves outcomes of liver transplant	Reduces EAD (3), may reduce early complications in DCD-grafts (5). Long-term complications are not different and under-reported (10)
		Likely no difference in graft loss or survival up to 1 year (7). More data needed
	Is cost acceptable due to improved complications	90-day costs are not higher in a risk-matched US cohort (5)
		More cost efficiency analyses are needed

NMP, normothermic machine perfusion; NAS, non-anastomotic biliary strictures; EAD, early allograft dysfunction; SCS, static cold storage; DCD, donors after circulatory death.

conclusions about the impact of NMP is challenging (*Table 1*).

Furthermore, the study lacks standardized reporting of complications using validated metrics, including the Clavien-Dindo Classification or Comprehensive Complications Index (12-14).

Prior works have emphasized these metrics specifically in machine perfusion research, as they are directly linked to long-term outcomes and costs of medical care. This concern is pivotal in navigating the advancement of this promising yet costly technology (15). Standardized reporting of donor/recipient risk and outcomes would facilitate cross-study comparisons.

In addition, incorporating liver transplantation-specific metrics, so called Core Outcome Sets (COS), defined in previous benchmarking studies could enrich posttransplant outcome assessment (16,17). Detailed reporting of complications, including anastomotic strictures (AS), NAS, vascular complications, post-transplant renal-replacement therapy, and acute rejection would enhance reproducibility and comparability across studies with different preservation techniques.

For instance, NAS represents an objective and clinically-relevant outcome directly linked to donor and graft risk. Its inclusion in reporting with enough detail would enhance comparability with future studies. While Yamamoto *et al.* reported IC rates, it does not distinguish them from bile leaks, complicating interpretation. Moreover, although graft loss is documented, the specific causes are not detailed, which would provide valuable insight. This critique aims not to question the validity of the findings, but to underscore the challenge to replicate research lacking standardized definitions and relying on panel judgement. This study is not alone in its variable outcome reporting; indeed, all available 11 randomized controlled trials (RCTs) on machine perfusion have reported different sets of "most

important" outcomes for liver transplantation, assessed at varying time-points (2-4,18-26). We encourage Yamamoto *et al.* to conduct an updated analysis incorporating benchmark outcomes to facilitate comparisons with future research endeavors.

Despite the study's focus on standard risk cohorts within benchmark criteria, elucidating outcomes comparisons between groups is challenging due to inherent differences in patient characteristics and procedural factors (16,17).

The authors assert that OCS enables them to transplant higher-risk livers (both extended-criteria DBD and DCDs), citing previous trials supporting this claim. However, the data from this study indicate that both groups generally fall within benchmark criteria.

Given the differences between study groups (SCS *vs.* NMP), including preservation time, hepatitis C status, distance from hospital (DCD-grafts) and high-risk donor status, it is difficult to make reasonable comparisons. Additional risk scores for donor and recipient risk [Donor Risk Index (DRI) (27), balance-of-risk (BAR) (28,29), or UK-DCD (30)] and/or propensity score matching (or similar) could help ensure equal risk distribution among study cohorts.

While the findings in this study are intriguing, they also raise concerns about resource utilization. TransMedics OCS® offers various "service packages", including organ recovery specialists. Were these utilized in the study? Additionally, the authors do not address the cost of these services, which is a significant limitation for many hospitals nationwide. Recent work using a risk-matched approach has demonstrated that back-to-base NMP is associated with improved short-term outcomes without increasing medical care costs (5). We encourage the authors to conduct a thorough cost analysis comparing care under SCS and upfront NMP. Such an analysis has not yet been published and should compare short- and long-term cost viability of different NMP approaches.

Given that both arms of the study demonstrated similar graft and patient survival, a less costly approach might be necessary for most hospitals. EAD is commonly used yet is not strongly linked to definitive patient outcomes. Thus, a more expensive approach to NMP that improves EAD but does not affect long term outcomes, might not be cost-justified. Dutkowski *et al.* noted that surrogate markers of liver injury such as transaminase release should not be used as primary endpoint, because their correlation with outcomes, especially in DCD liver grafts, is inconsistent (15). They also stated that "*defining liver graft dysfunction based on peak transaminases combined with later (e.g., 7-day) single levels of the international normalized ratio and bilirubin at arbitrary cut-off points must be avoided in perfusion trials*" (15). The Boston group should be commended for their approach in the PROTECT trial, which investigated the association of EAD with longer-term outcomes (2). However, since EAD frequently resolves, improving EAD alone might not lead to significantly better patient outcomes and could be quite costly depending on the specific NMP technique applied. Therefore, conducting a cost analysis would be highly beneficial, and we encourage the authors to pursue this as described.

The Yamamoto study advocates that upfront NMP can improve outcomes, particularly NAS, while end-ischemic NMP cannot (1). They cite a case involving 3,000 miles of travel to procure a liver graft, noting it was only feasible due to the device-to-donor aspect (upfront NMP). However, to date, only two studies comparing upfront and end-ischemic NMP with subsequent liver transplantation have been published, which showed no difference in outcomes for within-benchmark liver grafts (8,9). The assertion that upfront outperforms end-ischemic NMP is based on extrapolations of biliary complication rates from studies involving different donor and recipient risk and allocation systems on different continents. Additionally, these studies have had varied outcome measures and follow-up periods. We believe this conclusion is problematic, as it may influence national practice based on comparisons of fundamentally dissimilar studies.

The discussion of NMP outcomes (upfront/device-to-donor *vs.* back-to-base) raises questions about the future of perfusion with the potential advent of hypothermic oxygenated perfusion (HOPE). Studies from the US and Europe have demonstrated that HOPE can reduce NAS-rates despite equivalent cold ischemic time (CIT) in the SCS and HOPE groups (7,22,31). This occurs secondary to the protective effect of oxygen reintroduction at hypothermic temperatures, which reduces reactive oxygen species (ROS) and protects from mitochondrial damage. Such a protective mechanism has not been demonstrated in NMP, leaving the reason for a reduction in NAS unclear. The authors hypothesize that this is secondary to a reduction in CIT between groups. We argue that this study does not provide clear evidence that OCS offers benefits other than reducing CIT, which is certainly valuable. We encourage future studies to compare transplants with OCS and SCS with similar CIT, to assess whether ischemic time, perfusion, or both impact clinical outcomes.

The study raises the intriguing point regarding graft "non-use" due to rising perfusate lactate levels (n=5) and other concerning viability testing. We commend the authors for reporting this and for their willingness to discard grafts during perfusion, as viability assessment is one of the most promising benefits of machine perfusion. It is also important to note that the discarded grafts were from DCD donors, pointing towards increased risk and reperfusion injury despite short SCS prior to NMP. We also emphasize the need for robust markers for viability assessment as they are generally lacking. Of note, primary nonfunction and graft loss due to NAS were reported by others despite passing all traditional viability tests (including lactate clearance), particularly when risk factors exceeded benchmark criteria (10,11,32,33). Developing and validating both traditional and new markers will enable the safe increase in the use of organs traditionally deemed unsuitable.

Flavin-mononucleotide (FMN), a marker of mitochondrial injury, has been described for viability assessment during machine perfusion (34,35). Other clinical, perfusate and bile parameters have also been described, but few have been validated. Only the VITTAL trial has prospectively used most of such traditional criteria to assess liver injury (10,11,34-42). These studies highlight that factors beyond warm and CITs play a role, such as the underlying metabolic quality of the liver, which affects its resistance to transplant injury. This inherent quality is often unmeasured and underappreciated in most studies on machine perfusion, potentially explaining why the "ideal" CIT contributing to NAS varies widely between studies (4, 6 and even 8 hours), as livers likely have different levels of tolerable ischemic injury. Yamamoto *et al.* are in an excellent position to lead the field of viability assessment given their extensive experience with NMP. We hope that future studies from this group will advance this specific field to the next generation.

In summary, we thank and commend the Boston group for their ongoing hard work on this challenging but critical topic. We look forward to follow-up studies addressing further important points, including cost-effectiveness, viability assessment, and more. We hope that future or adjunct studies will employ techniques for risk-matching, as current comparisons have not involved groups with similar known risk factors. Additionally, they might consider assessing the impact of the OCS device in outside-benchmark cases, and reporting outcomes using a more standardized and rigorous approach. Upfront and back-to-base perfusion are both highly interesting topics, and we are eager to see how the field develops in the coming years. Along with the introduction of HOPE technology, each study raises new questions, and ongoing re-assessment is key to improving patient care.

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Footnote

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