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Response to Comment on: "Impact of Back-to-Base Normothermic Machine Perfusion on Complications and Costs: A Multicenter, Real-World Risk-Matched Analysis"

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We sincerely thank Walter et al[1] and the Charité team for their thoughtful review of our study.[2] The authors raise interesting points, and we generally agree with all considerations.

First, and most critically, the authors question whether our findings of decreased complications and cost neutrality with normothermic machine perfusion (NMP) are applicable to other types of dynamic preservation techniques. As they note, there are potential benefits of hypothermic-oxygenated perfusion (HOPE), with meta-analyses demonstrating significantly improved graft survival at 1 year as well as decreased incidence of major complications (Clavien–Dindo ≥3b).[3] HOPE-treated grafts also experience significantly lower rates of biliary complications, likely secondary to mitochondrial reprogramming which mitigates ischemia–reperfusion injury-induced biliary strictures.[4,5] Similarly, meta-analyses have demonstrated a lower incidence of primary non function and improved 1-year graft survival with normothermic regional perfusion (NRP), specifically within a donation after circulatory death cohort.[6] However, the grade of evidence is not as strong as no randomized control trials have been performed comparing NRP to cold storage or other perfusion techniques in a cohort with the same risk profile.

As Walter et al[1] correctly note, our most critical finding was that NMP was cost-neutral despite the additional upfront equipment costs due to a reduction in downstream complications. Our group has further demonstrated significant cost-savings on the waitlist, and in "dry run" costs with our NMP program, stemming primarily from an increase in the number of useable grafts and associated viability testing.[7,8] The impact of HOPE on cost has been examined in 2 small cohort studies.[9,10] As with our study, despite the additional upfront costs, the overall cost for HOPE was, at worst, similar to the static-cold storage (SCS) cohort, with the recent study by the Groningen group, Endo et al,[11] demonstrating a reduction in costs of intensive care unit and nonsurgical interventions in the D-HOPE group. HOPE is not yet Food and Drug Administration (FDA)-approved within the US Medical System, with such approval expected in 2025, we anticipate that HOPE will further improve post-transplant outcomes, reduce complications, and have a significant impact on cost savings with an expected lower cost per use, particularly compared with upfront NMP. No studies have examined the impact of NRP on postoperative healthcare costs, though consumables are generally estimated at $2500 to $3500 in European studies.[12] NRP also impacts severe grafts from the same donor, likely improving the cost profile, and future studies should take this into consideration when examining the cost associated with NRP.[13] However, we emphasize that a formal cost study with risk matching is needed for this approach. Conversely, NRP also does not have a clear viability assessment, and thus grafts may require NRP plus ex situ perfusion, which might contribute to cumulative costs, which should also be considered. Preliminary data on both NMP types, end-ischemic and upfront device-to-donor, seems to support a reduction in early complications, although the cost-per-use anecdotally varies significantly between these approaches and the downstream effects of device-to-donor has not been reported in any study of which we are aware.[14]

Walter and colleagues correctly point out that long-term data is necessary to convince system-level stakeholders of the validity of dynamic preservation, as also suggested previously by Boteon et al.[12,15] Interestingly, such data is more available with HOPE, recently published by Czigany et al[16] and Eden et al[17] separately, supporting long-term outcomes improvement with HOPE. Mergental et al[18] and Hefler et al[19] showed similar findings within back-to-base NMP. Such studies must be replicated within the US system with a focus on cost-effectiveness and quality of life; our group plans these studies imminently, both regarding NMP versus cold storage (SCS) and subsequently NMP versus HOPE when both technologies are available.

Our center has pursued back-to-base NMP now in >85% of cases based on the findings that it is relatively cost-neutral, allows viability assessment, and improves short-term outcomes. However, we also encourage ongoing reassessment of this approach as HOPE is introduced, additional long-term outcomes are accrued, and knowledge about which liver grafts require perfusion are developed.

In addition, the ongoing improvement of viability assessment parameters plays an important role. Briefly, flavin mononucleotide is a marker of mitochondrial complex 1 damage released during reoxygenation. Flavin mononucleotide was first validated in liver transplantation in HOPE and has now been validated in our center in NMP as reducing complications with publication pending.[5,20,21] We hope such an assessment is the intervention most likely to improve outcomes and reduce cost

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through selective discard of livers that are most likely to result in poor outcomes.

Finally, we believe similarly to Walter and colleagues that multiple cross-institutional large studies comparing HOPE, NMP, and SCS are essential to guiding long-term policy. We want to emphasize the utility of the "Core Outcomes Sets (COS) in Liver Transplantation" as a new tool that may aid with such a comparison.[22] Previous studies of all types of dynamic preservation are limited by their selection of different endpoints and timeframes for outcome reporting, as well as nonstandard definitions for similar outcomes.[16,23] For example, less than half of preservation trials to date have separately reported biliary stricture subtypes from bile leaks, which clearly have very distinct etiologies and outcomes.[14,22] The COS consists of 10 transplant-specific metrics plus 3 general metrics, which include intensive care unit/hospital length of stay and Clavien–Dindo complication scoring with associated Comprehensive Complication Index. These also reflect process measures that can address the points raised by Walters and colleagues. We encourage the use of this COS in future studies and, as suggested, the incorporation of quality of life/patient-reported outcome measures to best understand both the short-term and long-term impact of these approaches.[22]

We again thank Walters and colleagues for their thoughtful review and agree wholeheartedly with their assessment and encourage multicenter comparison studies including all mentioned aspects.

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