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**Re: Biliary Bicarbonate, pH, and Glucose Are Suitable Biomarkers of Biliary Viability
During Ex Situ Normothermic Machine Perfusion of Human Donor Livers**

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Conflicts of Interest: The authors declare no conflict of interest.

ACCEPTED

To the editor:

We read with great interest the recent study by Matton et al published in Transplantation in November 2018.¹ The authors used normothermic machine perfusion to assess 23 livers declined for transplantation and showed that biliary bicarbonate and pH were significantly higher and biliary glucose was significantly lower in livers with low bile duct injury (BDI). The conclusions confirm previously published results about the importance of bile pH and bile glucose as markers for BDI assessment in donors after brain death (DBD) and circulatory death (DCD).^{2,3} However, some important points require discussion. To assess for BDI, the authors combine the factors from their original paper (injury of the deep peribiliary glands, the peribiliary vascular plexus, and mural stroma necrosis)⁴ into a score that they use as a surrogate for non-anastomotic strictures. The original paper did not have such a combined score, therefore the use of this ad hoc score is not known to predict for non-anastomotic strictures in the clinical situation. Further investigation should analyze these parameters in conjunction with the individual histologic findings or demonstrate that the combined histologic score has predictive ability greater than the individual histologic components based on the outcomes in the original paper. In their study the authors did not reveal the reasons why these livers were declined and whether they were declined before or after the donor procedure. This seems of importance, since these clinical biomarkers cannot be validated in a heterogeneous population (including DCD and DBD) that does not match the actual liver pool used for transplantation. Another important point is the understanding and investigation of the causes of bile injury. Donor age and cold ischemia time exceeding 8 hours have been previously demonstrated to be associated with the development of ischemic cholangiopathy in recipients of DCD livers.⁵ In addition to these two factors, we believe that excessive liver cut out time (>30 minutes) during the donor operation may also increase the incidence of BDI

(unpublished data), in addition to being deleterious to immediate liver graft function.⁶ Given the latter, it would be of much interest for future studies to collect the preclinical donor data and stratify for the high/low BDI groups in order to identify the potential causal factors for bile injury.

The last step will be to determine if a liver can be safely discarded or transplanted based on the estimated risk of developing BDI. To answer this question, a randomized controlled trial including a larger and homogeneous cohort of patients would be warranted. The use of biliary pH, glucose, lactate dehydrogenase and bile duct histology on frozen section as a preimplantation diagnostic tool could be compared to standard of care.

If this is achieved, such a tool may ultimately be used to increase the donor pool, by allowing safe selection from suitable organs among extended criteria livers without significantly increasing the risk of biliary complications. With this in mind, one should concomitantly attempt to identify and reduce modifiable risk factors for BDI in order to further minimize the incidence of biliary complications.

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