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In Reply

We thank Dr. Okumura, Dr. Dhand, Dr. Misawa, and Dr. Nishida for their thoughtful responses to our recent article. (1) In their response, they highlight critical points regarding variable selection, interaction between variables, and additional sub-analyses that might provide additional insight into the mechanism of post-transplant AKI.

As the letter writers suggest, understanding the confounding effect of the Model for End-Stage Liver Disease Score (MELD) was something our study authors discussed extensively. Because patients developing AKI had lower MELD (18.0, SD 7.1 compared to 19.7, SD 8.8, *P* <0.001) on *univariate* analysis, which conflicted with previous studies showing higher MELD predicting AKI in some,(2–4) but not others;(5,6) we ultimately felt the impact of MELD was worth investigating in our *multivariable* regressions. We felt justified with this decision since the variance inflation factor was less than 2 for all covariates, including the risk factors noted by the

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responders: MELD, BUN and eGFR. Although the suggestion to exclude high MELD patients from the study is certainly reasonable, we feel that since MELD was not ultimately selected in the multivariable models - this is unlikely to significantly change the study results. We also appreciate the excellent insight regarding lower MELD patients (often with hepatocellular carcinoma) - might have a higher probability of receiving a liver transplant from a donation after circulatory death (DCD). In response to this suggestion, we note that only 7% of patients received a DCD and that neither covariate (DCD donor or MELD score) ultimately appeared in any of the multivariable regressions (Model 1, 2, 3, 4, 5, or 6). Future studies on a larger multicenter population of transplant recipients, might quantify the interaction term between DCD and MELD.

We agree that resolving specific risk factors associated with dialysis requirement would be very interesting. As only 19 patients (3%) required new postoperative dialysis, we are, unfortunately, underpowered to assess risk factors in a multivariable analysis. This limitation of our single-center study, highlights the necessity of integrating multi-center data to study low-frequency outcomes, a future goal of our combined approach.

Additionally, the impact of intraoperative factors alone becomes very difficult to analyze when evaluating AKI for up to 7-days post liver transplant. In fact, one of the major conclusions of our study was that the overall improvement in discrimination by adding intraoperative data is minimal. We hypothesized that this may be because renal injury has already occurred, by the time intraoperative data are collected. As the letter writers point out, such analysis may be further complicated since these defined risk factors are not chronologically one-off events, are often overlapping and may exert a cumulative effect.

Finally, expansion of the variables collected will undoubtedly improve model quality. A strength of our methodology is the standardization of reportable variables and outcomes: Multicenter Perioperative Outcomes Group (MPOG) and Organ Procurement and Transplantation Network (OPTN). Our hope is that this methodology can be easily scaled to capture a larger cohort for future studies. Inclusion of additional variables include prior episodes of systemic infection impacting end-organ perfusion, pulmonary hypertension, recent intravenous contrast use, types of anti-hypertensive medications, nutritional status, and albumin supplementation may ultimately require institution-specific data query and manual review, which exceeded the scope of this preliminary study. Furthermore, covariates not currently available in OPTN data could be collected to help refine our understanding of donor quality and its important influence on perioperative renal injury.

In conclusion, we thank Dr. Okumura, Dr. Dhand, Dr. Misawa, and Dr. Nishida for their valuable feedback to our recent article. Although the addition of certain variables may provide additional insight into the pathophysiology of post-transplant AKI, the risk factors demonstrated in our single-center pilot study remained remarkably consistent across multiple models (censored to variable class and phase of transplant). Furthermore, the impact of MELD, and the necessity of accounting for interaction between MELD and variables like DCD remains an interesting area for continued research that was not explored in more depth since MELD did not

occur in the final regressions. Additionally, to appropriately power some interesting sub-analysis, such as patients requiring postoperative dialysis, we must dramatically expand patient numbers through multicenter integration, which remains a focus of ongoing work from our team. Finally, even if adequately powered, the overall improvement in discrimination by adding intraoperative data likely remains modest in comparison to donor and recipient factors.

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