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Response to Comment on: Age Matters: What Affects the Cumulative Lifespan of a Transplanted Liver? Continued Yet Cautious Expansion of Donor Age in US-Based Liver Transplantation

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We thank Drs Akabane, Sasaki, and their team for their thoughtful review of our article "Age Matters: What Affects the Cumulative Lifespan of a Transplanted Liver?"[1] We appreciate their insights[2] and commend their work on donor–recipient age differences in liver transplantation outcomes.[3] A few points should be addressed:

The supply–demand mismatch in liver transplants has driven interest in using traditionally "high-risk" grafts to expand the donor pool.[4–6] Dynamic preservation techniques are facilitating these practices, as seen with routine use of hypothermic oxygenated perfusion in Europe for many years[7,8] and more recently here in the United States with the implementation of normothermic machine perfusion.[9,10] However, as the Stanford team noted in their 2023 study, proper donor–recipient matching remains key.[3,11,12] They identified a difference comparing their analysis to ours, which we are not able to explain with our current data. While perhaps our conclusion has been optimistic, we highlight encouraging evidence, supporting the use of older and very old donors. Akabane et al noted that transplanted livers often achieve longevity like the general population despite the transplant injury. This finding while not directly guiding donor or recipient selection offers valuable insights into subcellular liver injury. Our analysis of the national cohort showed no impaired graft survival for donors over 70 years, compared to younger livers, even when used for recipients under the age of 70 years (Fig. 1).

We also highlight interesting parallels from European practices where the use of older donors is more routine. Italian surgeons recently transplanted the first case from a 100-year-old donor.[13] In 2008, Italian practice had employed a 94-year-old donor and was advocating for "no donor age limit" in liver transplantation.[14] More recently, outcomes have been generally reassuring with the use of octogenarian donors with remarkable patient and graft survivals, despite a higher rate of biliary complications in this group when preserved with static cold storage.[15–17] Specifically relevant to US practice, Ghinolfi et al report a set of risk factors that are associated with biliary complications in octogenarian donors, including cardiovascular donor instability and recipient disease severity (lab Model for End-Stage Liver Disease score).[17] These findings, along with the expanding use of machine perfusion and robust viability testing, suggest that donor age may be cautiously expanded in the US population, as currently seen at our center. The Food and Drug Administration approval of devices for hypothermic oxygenated perfusion techniques is eagerly anticipated to further expand the aged donor pool while limiting biliary complications, and the needed interventions, as seen in Italy.[8]

We acknowledge the selection biases in our approach, which aim to generate preliminary data supporting the use of older donors. Each liver is metabolically unique and affected by the donor's lifestyle and environment. Thus, a 70-year-old graft from a particular donor may function like a 30-year-old graft from another. Predicting these differences remains challenging limiting the expanded use of older donors. We hope markers of metabolic and mitochondrial injury, such as flavin mononucleotide, might help.[18,19] Our group is working on projects to identify hepatocellular and cholangio-cellular senescence before transplant.

We appreciate the follow-up time recommended by Akabane et al. We included data up to 2022 to reflect the modern practices of using older donors in the United States, despite potential bias compared to earlier eras. Our study aimed to highlight the oldest achievable ages in various categories and assess graft outcomes in higher risk populations as "hypothesis-forming" rather than "practice-changing" research. Among the 34,656 grafts transplanted in the final 4.7 years of follow-up, up to 700 (2.0%) achieved a cumulative age of >80 years, 103 (0.3%) over 90 years, and 5 achieved an age of >100 years. While this inclusion introduces limitations, it also provides valuable insights.

In conclusion, we thank Akabane et al for their thoughtful review. We look forward to further exploration in liver aging and transplant injury. While our study has limitations and aims to generate new hypotheses rather than guide clinical decisions, we believe it raises important questions about the future of transplantation and hope it inspires ongoing research in this field.

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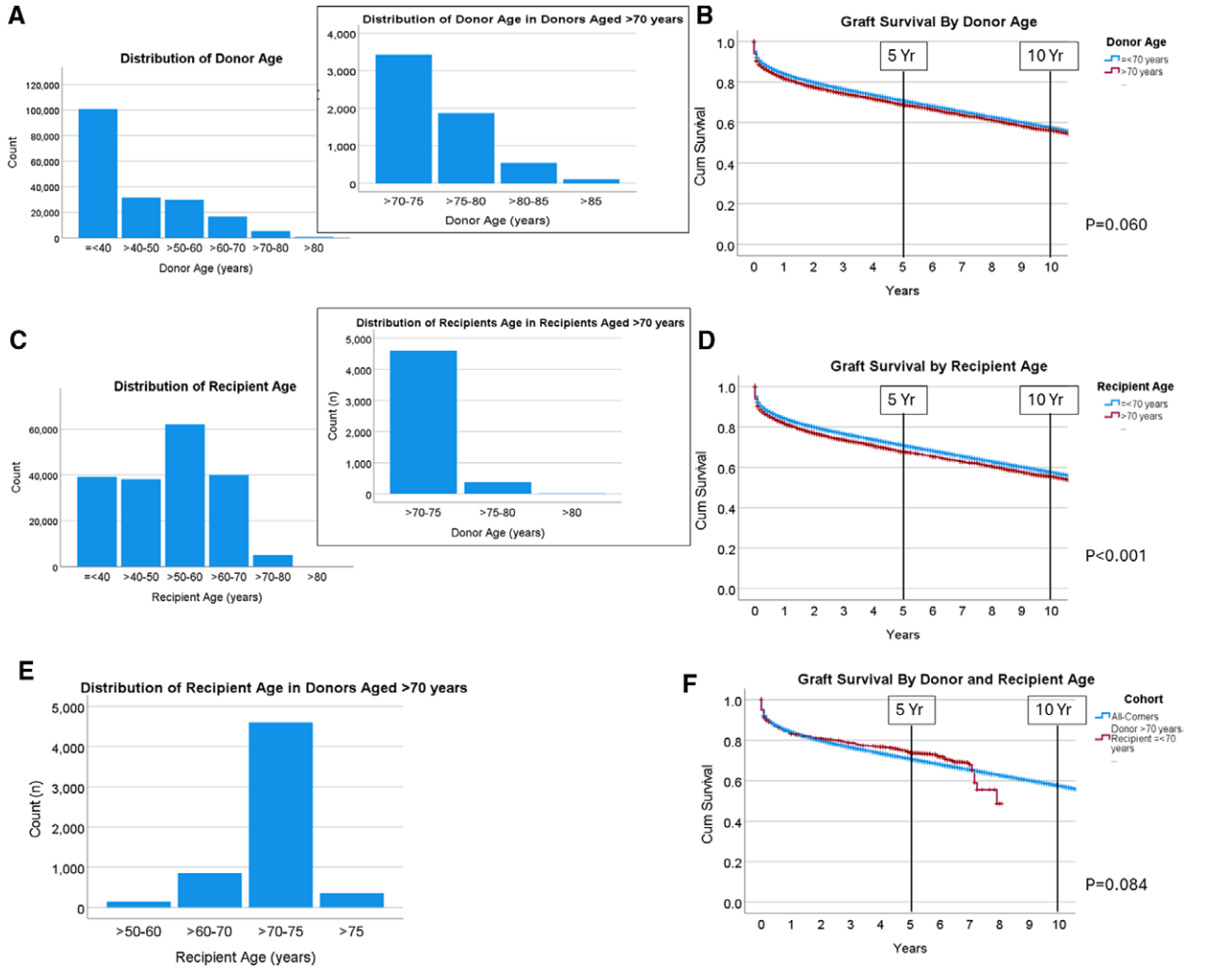

FIGURE 1. Graft survival and distribution of liver transplants in donors and recipients beyond the age of 70 years. There were 5949 transplants originating from donors >70 years and 4991 to recipients >70 years; 993 were from donor >70 years transplanted to a recipient <70 years.

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