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Response to Comment on: Age Matters: What Affects the Cumulative Lifespan of a Transplanted Liver?

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We would like to thank De Simone and Lai for their thoughtful review of our article titled "Age Matters: What Affects the Cumulative Lifespan of a Transplanted Liver?."[1] Their considerate review is poignant, well-written and insightful.[2] In response to their suggestions, we do have a few thoughts.

First, the assertion that cumulative liver age will be longer in older donors even if graft survival is poor is certainly accurate. This study began as an investigation into how liver transplantation (LT) affects the aging of liver grafts given the inherent injury associated with transplant. Indeed, we reported that "the donor age is the major contributor to cumulative liver age in all recipient and donor decades of life."[1] We chose to compare the population of transplanted livers to the greater population of the United States as a mechanism to place the calculated cumulative liver age in the context of the general population. However, as De Simone correctly reports, there are regional variations in life expectancy,[3] and the analysis could therefore be more granular in comparing cumulative survival after LT in subregions with general survival in the corresponding region. We agree this would be a meaningful analysis, and fully plan to work on a follow-up study with this aim.

The authors suggest comparing the achieved cumulative liver age for each included donor age to the predicted life expectancy for an otherwise healthy individual of the same age. We find this to be a poignant suggestion and intend this as a follow-up study. As De Simone and Lai note, the median donor age in our study was 37 years. The average life expectancy for a healthy 37-year-old is 39.62 years, with just a 0.29% probability of death within 1 year.[4] All-comers in our study would have a median life expectancy of 4.7 years (interquartile range: 1.1–10 years), and a 20% chance of death within 1 year.

However, we want to emphasize that our study was focused in some capacity on the exceptionally well-achieving livers. Liver transplant outcomes are uniquely multifactorial. Compared with a healthy individual, transplanted livers must contend with not just donor factors, but also recipient disease, transplant injury, and long-term immunosuppression. Indeed, their recent work on the topic, titled "Aging with a Liver Graft: Analysis of Very Long-Term Survivors after Liver Transplantation," clearly details accumulating complications associated with chronic immunosuppression in very long survivors after LT.[5] Thus, a direct comparison of these 2 life expectancies is not comparing equivalent factors. However, the stated fact that young death disproportionately affects life expectancy, and that stratified reiteration of the data by donor age might be additive, both resonate strongly with us, and we intend follow-up studies with both aims.

Finally, De Simone and Lai discuss the very interesting issue of regional variation in donor age. Their impressive previous work details clearly that donor age in European countries such as Italy are nearly double those in the United States.[5] Eden et al further detailed international variations in not only age, but additional risk factors, strongly showing that donation after circulatory death utilization and acceptable risk vary widely from United States versus European countries, and indeed even between European countries.[6] As such, we find regional reanalysis to be highly relevant, with one key caveat. Our study was conducted using only LT within the United States, and practices within the United States are somewhat more homogenous than practices across Europe, as the United States is one country with a nationally governed allocation policy (vs Europe with many countries), and programs are judged nationally on their outcomes using the same criteria. This is not to deny regional variances, but to say that our dataset would only allow for within-country regional variances, which would not capture differences between, say, the United States and Italy. However, a follow-up international study of liver aging in LT would be of relevance and we will investigate the feasibility of this approach also.

In conclusion, we appreciate the review and comments of De Simone and Lai. We agree with their conclusions, and their comments have given us ideas for future studies we think can help add to the knowledge base on this topic. Our study is a preliminary, first-report of the encouraging outcomes that can be achieved in LT. We view our work as the "first chapter" rather than the last and will be excited to work diligently with De Simone, Lai, and others to further expand the international knowledge on the subject.

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