

## **To Editor**

Thank you for the opportunity to revise our manuscript. In response to your feedback, we have refined our analysis by removing some statistical methods, specifically the Cox regression and mediation analyses, to focus primarily on the competing risks approach. This adjustment has streamlined the clinical interpretation for the reader, ensuring clarity without compromising the depth or significance of the findings.

We also revised the discussion section to better align with the reviewers' suggestions, emphasizing our study's key insights and implications. This study makes a valuable contribution by highlighting significant inequalities in access to deceased donor kidney transplantation in Brazil, and we hope it will inform future efforts to address these disparities.

## **Deputy Editor: 1**

### **Comments to Author:**

**The authors provided retrospective registry data from the Brazilian National Transplant database to analyze deceased donor transplant rates from different locations and demographics between 2012-2022. They concluded "We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation." Brazil, a large multi-racial country with over 200 million population of varying socioeconomic status would appear to be a good comparator for similar trends as the USA. That said, the reviewers detail important distinctions in the analysis that require direct responses to help generate focus and a message that translates into clinical guidance for the Discussion. In addition, from personal experience, there are massive problems with transportation in certain areas of Brazil, especially the densely populated Sao Paulo region with the majority of large transplant centers. What role do the efficiency, cost, and travel times for candidates distant from transplant centers play in accessing deceased donor transplantation?**

We agree that transportation challenges, especially in densely populated areas like São Paulo, play a significant role in accessing deceased donor transplantation. Efficiency, cost, and travel times can pose substantial barriers for candidates who live far from transplant centers. Although our current analysis did not specifically account for transportation issues, we recognize that this is a critical factor influencing access to transplantation. Most transplant centers in Brazil are located in urban areas, and candidates from rural or distant regions may face significant logistical challenges in reaching these centers. This not only affects their ability to undergo necessary evaluations and procedures but may also impact their inclusion on the transplant waitlist and their availability for organ offers.

## **Associate Editor: 2**

### **Comments to Author:**

**1. "Regional Disparities in Kidney Transplant Allocation in Brazil" presents a comprehensive and rigorous analysis of kidney transplant allocation disparities. While the academic rigor of the work is commendable, the style of reporting is ambiguous about whether the authors seek to describe the statistical significance of their findings, the**

**clinical relevance, or whether they seek to make a public health statement and possible intervention. For instance, if only 0.5% of observed effects are mediated by geographical region, why is it "urgent" to implement approaches to enhance transplant capacity in the North region? On the other hand, if a care-provider is communicating the likelihood of transplantation to an individual from the North, then surely a sHR of 0.38 is all that matters (not the metric from mediation analysis).**

Thank you for your valuable feedback. We understand the importance of clarity in presenting our study's focus and the implications of our findings.

The primary analysis conducted in our study was a competing risks analysis, which considered death and removal from the waitlist as competing events. This approach allowed us to accurately estimate the subdistribution hazard ratios (sHR) for the likelihood of receiving a deceased donor kidney transplant (DDKT) while accounting for the competing risks patients face while on the waitlist.

To enhance the clarity of our results and discussion, we removed the Cox regression and mediation analyses from the study. By focusing solely on the competing risks analysis, we aim to present a more coherent and focused interpretation of the disparities in kidney transplant allocation. Our discussion and interpretation of results are now centered on the sHR derived from the competing risks analysis.

**2. The meticulous approach is evident in the detailed reporting of outcomes by various risk factors, presented through univariable, adjusted hazard ratios (HR), and adjusted subdistribution hazard ratios (sHR). The aesthetically pleasing cumulative incidence curves further illustrate these findings, albeit they parallel the univariable HR from the tables, making the output redundant. What is the purpose of reporting so many metrics that it makes interpretation difficult for the average clinician? Why univariable HR, aHR from Cox regression, and sHR from competing risks? Are all conveying information central to the narrative? Can the reporting be more focused?**

We acknowledge that presenting multiple metrics may complicate the interpretation for readers, particularly clinicians who may not be as familiar with the nuances of these statistical methods. We reviewed the results by focusing on the sHR from the competing risks analysis, which is most relevant to the study's primary objective of assessing disparities in transplant allocation. We removed the univariable and multivariate Cox regression from the main tables and focused on the adjusted sHR in the results section. We retained the cumulative incidence curves, as they visually complement the sHR findings, but we ensure that the interpretation aligns closely with the narrative focused on competing risks.

**3. If the reader has to put the findings of this paper in the context of their entire clinical profile rather than adjusted risk factors, critical issues emerge. First, several risk-factors have HRs that are statistically significant but close to 1 (e.g., gender and ethnicity). Others, such as time on dialysis, are difficult to interpret in a clinical setting (e.g., what does HR=0.97 for someone who has been on dialysis for 5 years?). On the other hand, there are striking risk factors such as cPRA > 90% with HR=0.29, south region with HR=2.53, and north region (HR=0.38). So regardless of mediation analysis or statistical significance of a given risk factor, these characteristics will have very noteworthy implications in a given clinical scenario, which is the combination of all these risk factors**

**and interactions. No patient or care provider is testing a hypothesis on an isolated risk factor that isn't under the control of the patient, such as region. So the authors should keep their narrative informative by clarifying the context they wish to inform. If the authors seek a public health intervention with a focus on regions, then much of the analytic output is way too distracting. A more focused narrative would help the reader.**

Thank you for your constructive feedback. We understand your concerns about the clinical relevance of the findings and the need for a focused narrative.

We acknowledge that some risk factors, such as gender and ethnicity, have HRs close to 1, indicating only modest effects. However, these findings are statistically significant and point to subtle yet important disparities that may contribute to inequities in transplant allocation. On the other hand, risk factors such as cPRA > 90%, regional differences, and time on dialysis show more pronounced effects and have clear clinical implications.

We reduced the emphasis on risk factors with sHR close to 1. We concentrated on the most clinically and public health-relevant findings, particularly the striking regional disparities and their implications for healthcare access and equity.

Combining all these risk factors into a single clinical decision tool can be challenging. Developing a calculator that integrates these factors to predict waiting list time could significantly enhance the utility of our findings in clinical settings. However, as this was not the objective of the current study, we did not pursue this approach at this time.

In a previous study, we developed a machine learning model specifically for the state of São Paulo to predict time on the kidney transplant waiting list. This model incorporated various predictors and was implemented in an API-based calculator, which has proven valuable in clinical practice (doi: 10.1371/journal.pone.0252069). Future work could extend this approach to a national level, incorporating the comprehensive data and findings from this study to support clinicians and improve patient outcomes across Brazil.