Author’s response to reviews

Title: Prevalence and Correlates of Cognitive Impairment in Kidney Transplant Recipients

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Author’s response to reviews:

Dear Dr. Piccoli,

On behalf of all the authors, I would like to thank you and the reviewers for the insightful comments on our manuscript ‘Prevalence and Correlates of Cognitive Impairment in Kidney Transplant Recipients’. We have revised the manuscript with careful attention to your suggestions. Our responses (in italics) to the reviewers below include all the editor’s comments.

Sincerely,

Aditi Gupta

Response to comments by Reviewer 1.
1. ABSTRACT

a) line 17: Assessment of cognitive function I'd suggest to use cognition or cognitive functioning, or cognitive domains. Please choose the expression and correct the entire manuscript.

We have changed ‘cognitive function’ to ‘cognition’ throughout the manuscript.

b) line 51: level of GFR.

I'd suggest to write the meaning of the acronym before using it (Estimated GFR).

We have made this change in the revised manuscript.

2. BACKGROUND

a) I would find it helpful if the Author examined better the literature on the relationship between cognitive functioning and kidney transplant. There is some interesting papers that the Authors could be report:


- Tiffin-Richards FE et al. Plosone 2014. DOI: http://dx.doi.org/10.1371/journal.pone.0106700

These have now been included in the revised version. The paper by Gelb et al has been added in the background (reference 11). We have now included how Gelb et al identified cognitive impairment in specific domains of verbal learning, memory and executive functioning in kidney transplant recipients. The paper by Tiffin-Richards has been added in methods, under outcome variable (reference 21). The main text includes how Tiffin-Richards et al successfully used MoCA in kidney disease and found that it performed better than the MMSE, as MoCA is more sensitive is assessing executive function.

b) Line 11-12:

Please move the numbers before the point. Correct the manuscript.

We have made this correction in the revised version.

3. METHODS

a) Consider that MoCA assesses several cognitive domains and it is a useful cognitive screening tool for several diseases.

This has now been noted under outcome variable in methods.
The MoCA is a validated, clinic-based tool that samples from various domains of cognition and is sensitive in detecting mild cognitive impairment in several diseases, including Alzheimer’s disease and vascular dementia.

b) The presence of confounders like depression is not elicited, QI index and its association with the cognitive impairment was not studied.

We acknowledge these limitations in the discussion section. “Depression can affect cognitive performance but was not assessed in this study.”

c) There are no information regarding the patients' compliance and the adherence to the immunosuppressive therapy (for example through the evaluation of the hematic levels of the drug).

This is an important point and a great suggestion. The goal of this study was to present prevalence of cognitive impairment in kidney transplant recipients and assess the risk factors associated with cognitive impairment. We did not assess outcomes of cognitive impairment in this study. We agree that assessment of outcomes of cognitive impairment such as adherence is important and should be a focus of future studies.

4. DISCUSSION

a) I think that discussion needs to be more focused on covariates of cognitive impairment of this study and on possible explanations of the prevalence of cognitive impairment in transplant recipients. I believe that this part is not adequately elaborated.

We have revised the discussion to adequately elaborate on the covariates of cognitive impairment and the pathophysiology of cognitive impairment post transplantation. We have added the potential role of hemodynamic changes with dialysis, vascular alterations, chronic inflammation and comorbid conditions such as diabetes and hypertension.

Response to comments by Reviewer 2.

1. Study design does not allow to evaluate any changes in the score (considering data prior to transplant or after a defined follow up) and it does not allow to make any physiopathologic conclusions.

We acknowledge this limitation in the discussion (paragraph 8 in discussion).

‘The cross sectional design precludes conclusions regarding cause and effect and does not provide information on whether cognition is stable, improving or deteriorating. Furthermore, it does not allow comparison of current level of cognition with that pre-transplant, or the association of current level of eGFR with decline in cognition in follow up.’

The purpose of this paper was to study the prevalence of cognitive impairment after transplantation. Since our goal was to study prevalence, a cross-sectional study design is most
suited for this study. We agree that longitudinal studies of cognitive function in transplant recipients are essential to evaluate changes over time and risks for these changes.

2. Considering that no association between eGFR levels and MoCA score were noted. This does not make the results surprising since as authors state the prevalence of cognitive impairment in dialysis patients is well known and it is known to be more precocious compared to general population. Dialyzed patients are indeed exposed to many alterations and the metabolic alterations associated to uremic state are only the tip of the iceberg, making the hypothesis that cognitive impairment may as well be due to several other factors such as vascular alterations secondary to chronic inflammatory state or to diseases such as diabetes and hypertension more plausible.

We agree and appreciate these comments. In CKD, the degree of cognitive impairment is associated with the level of GFR. We therefore evaluated the association of GFR with cognition in kidney transplant recipients and noted that there was no association. As reviewer 2 pointed out, factors other than eGFR may be at play in causing cognitive impairment post-transplant and we therefore did not see the association with GFR. We now include more in the discussion as to why GFR may not be related to cognitive function, but why cognitive function is still impaired.

“This implies that the etiology of cognitive impairment in dialysis and kidney transplant recipients cannot be entirely attributed to a lower level of GFR but that other factors mentioned above contribute. Patients on dialysis are indeed exposed to metabolic and hemodynamic alterations that might contribute to cognitive impairment. Although there is an association with eGFR in pre-transplant CKD, cognitive impairment in this population may as well be due to several other factors such as vascular alterations, chronic inflammation and comorbid conditions such as diabetes and hypertension. It is also likely that cognitive impairment in pre-dialysis CKD takes several years to develop while level of eGFR in the transplant recipient only reflects a short period of the individual’s life-time exposure to cognitive risk.”

3. The proposed data thus is only minimally innovative and although it may be useful to consider the higher risk of cognitive impairment in transplanted population compared to general population the main bias is considering formerly dialyzed patients comparable to general population and also implying that a score below 26 can indeed condition a reduction of adherence to therapy.

We appreciate this comment. The published literature has primarily focused on dialysis associated cognitive impairment and the high prevalence of cognitive impairment in kidney transplant recipients (at least compared to general population norms) is underappreciated. Some studies indicate that cognition improves after transplantation (and may be comparable to the general population). Therefore, it is important to understand that there is a high prevalence of cognitive impairment in transplant recipients. We hope that studies such as ours will create more awareness of post-transplant cognitive impairment, so that efforts can be focused on strategies to help patients with cognitive impairment to allow them to experience complete benefits from renal transplantation. We also agree that evaluation of whether cognitive impairment affects adherence is an important area of future studies.
Response to comments by Reviewer 3.

1. It is not completely clear how model 2 was constructed: the authors reported that the included variables were selected according to changes in the adjusted R-squared from model 1. However, these values are not available. Please included these values, at least in Supplementary materials. Please specify adjusted R-squared and P-values of model 2 and of logistic regression.

We thank Reviewer 3 for noting this concern. We have now added the adjusted R-squared results, and the order in which the variables were removed from model 1 to build model 2 in supplementary data 2.

‘For model 2 we removed variables in the following order with the adjusted R-squares after removal of that variable in parenthesis: race (0.1480); ESRD secondary to diabetes (0.1520); stroke (0.1560); coronary artery disease (0.1598); time to kidney transplant (0.1636); eGFR (0.1665); BMI (0.1683); and blood pressure (0.1692). The remaining variables, i.e. age, gender, level of education, history of diabetes, history of smoking, history of atrial fibrillation, serum hemoglobin, diastolic blood pressure and time on dialysis prior to transplant were included in model 2.’

We have also modified our description in the methods section for the logistic regression model presented in this work. In table 3, we assessed the adjusted associations of the variables selected for Model 2 (in table 2) with a dichotomous outcome (cognitive impairment as indicated by a MoCA score of <26, or no cognitive impairment) using a threshold response measure (rather than a continuous MoCA score). Thus, we used an unconditional logistic regression model predicting cognitive impairment as indicated by a MoCA score of <26. This was more of a sensitivity analysis by looking at the same outcome measure in a different way (i.e., as a dichotomous measure rather than more continuous). Also, since this was a logistic regression model, we do not obtain an adjusted R-square result. The p-values for these variables from model 2, adjusted for other factors is presented in Table 3. We appreciate Reviewer 3 drawing attention to these issues, as they have served to improve our presentation of this work.