

March 11, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16644-review.doc).

We thank the reviewers for the time and expertise they have invested in our manuscript. We carefully considered your comments and we revised the paper based on those recommendations (highlights in manuscript). We are grateful for the opportunity to resubmit the manuscript

**Title: ESTIMATING GLOMERULAR FILTRATION RATE IN KIDNEY TRANSPLANTATION: STILL
SEARCHING FOR THE BEST MARKER**

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewers:

(1) "Glomerular filtration rate (GFR), is generally considered to be the best measure of graft function, and also an outcome predictor (**which outcomes?**)". We add "Glomerular filtration rate (GFR), is generally considered to be the best measure of graft function, and also a predictor of graft and patient survival."

(2) "However GFR measurement using exogenous markers (**such as...**)". The authors summarize the different GFR measurement markers, as "such as radiolabeled isotopes (51Cr EDTA, 99mTc DTPA or 125I Iothalamate) and non-radioactive contrast agents (Iothalamate or Iohexol)."

(3) When we emphasize that "decreased graft GFR is also associated with increased cost (**specify, please detail?**)", we want to say that it was generally associated with increased health care costs, so we add "Decreased graft GFR is also associated with increased health care costs, and over the two years, transplantation was both more effective and less costly than dialysis".

(4) "Some Cr is also incorporated from the diet (**some more details?**)". When we review the role of creatinine (Cr) as GFR marker, it is important to note that multiple factors contribute to reduce the accuracy of this marker, as the diet. Namely, meat ingestion contributes to the urinary Cr excretion, both as a result of expansion of the total creatine pool and as a result of gastrointestinal absorption of Cr.

(5) In kidney transplantation there are other factors that may impact on Cr tubular secretion, such as trimethoprim, and the authors add "Also, chronic rejection and acute tubular necrosis, can contribute, because tubular secretion of creatinine is reduced."

(6) The interest in Cystatin-based equations as an outcome predictor in kidney transplantation, was reinforced by the reviewers, indicated a very recent study examined the extent to which the addition of

serum cystatin C improves GFR estimation and mortality prediction, in comparison to various eGFR equations, in a population of liver transplanted patients [86]. We agree with this appointment, and a reference to this aspect was reported: “ Interestingly, very recently, a study examined the extent to which the addition of serum cystatin C improves GFR estimation and mortality prediction, in comparison to various eGFR equations, in a population of 401 liver transplanted patients. In this work, the authors founded that cystatin C, by itself or as a part of an eGFR, was a significant predictor of mortality [86].”

(7) In the analyses of creatinine-based GFR estimation equations performance in kidney transplantation, the authors noted that the systematic evaluation of the development methods of all Cr-based eGFR equations published recently, by Shaffi et al [57], may have implications in clinical practice, support the use of these eGFR equations to routine access renal function in transplant patients. However, this study has some limitations, not listed in our first review. So we decided to add “Even though was a good diagnostic test study design with a standardized reference test, the study population included few nonwhites and individuals with solid organ transplants other than liver and kidneys; therefore assessment of the equation performance in these subgroups is limited.”

(8) Finally, the reviewers raise an important issue: “ **The importance of proteinuria as marker of deterioration of renal function also in transplanted patients,...**” Although not a direct GFR marker, the proteinuria is also an important indicator of allograft dysfunction, so we have addressed this issue in the last part of our manuscript.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Nephrology*

Sincerely yours,

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