Author's response to reviews

Title: TITLE: Risk factors for acute kidney injury following orthotopic liver transplantation: the impact of changes in renal function while patients await transplantation

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Author's response to reviews: see over
RE: Manuscript for BMC Nephrology, Category Clinical Research paper

Dear Sirs

We are submitting the revisions (please see below under comments to reviewers) the manuscript entitled. Risk factors for acute kidney injury following orthotopic liver transplantation: the impact of changes in renal function while patients await transplantation. The NIDDK-LTD was established to study the demographics, clinical and laboratory characteristics, and outcomes of patients evaluated for and undergoing OLT. The NIDDK-LTD contains extensive pre- and post-OLT data for 916 recipients from 3 clinical centers: Mayo Clinic, Rochester, Minnesota; University of Nebraska Medical Center, Omaha, Nebraska; and University of California, San Francisco, California. The current study was designed as a retrospective cohort study. Of 916 patients enrolled in the NIDDK-LTD, 688 patients were included in our analysis. The results presented in this paper have not been published previously in whole or part, except in abstract form. The coauthors and respective contributions are as follows: Jose Iglesias D.O. Conception, design, analysis and interpretation of data, drafting the article revision for critically important intellectual content. John DePalma DO data design, review of literature and data abstraction. Jerrold S. Levine M.D., Conception, design, analysis and interpretation of data, drafting the article revision for critically important intellectual content.

Disclosures: Jerrold S. Levine, Research funding from Genzyme, Inc.

We are extremely grateful for the insightful comments of the reviewers with such excellent experience and credentials in the field.

Sincerely,

Jose I. Iglesias DO  FACP

Reviewer: Noel Gibney

Major compulsory revisions:

(1) "Transplant" is spelled incorrectly in Fig 1 and should be corrected. Fig 1 is somewhat confusing and the legend should be expanded to more fully describe this figure.
We have corrected the spelling in Figure 1, and thank the reviewer for catching this error. We have also expanded the legend, which now reads:

"Figure 1. Distribution of rates of change of serum creatinine (ΔScr/Δt_wait) while awaiting orthotopic liver transplantation (OLT) in patients who did or did not develop post-OLT acute kidney injury (AKI). Patients were stratified in order to according to ΔScr/Δt_wait and subdivided into deciles containing equal numbers of patients. ΔScr/Δt_wait was defined as the absolute change of serum creatine (ΔScr) while awaiting OLT (Scr pre-OLT minus Scr at registration) divided by the time awaiting OLT. The percentage of the total number of patients (n=243) who developed AKI (AKI) falling within each decile is plotted. Similarly, the percentage of the total number of patients (n=445) who did not develop AKI (NO AKI) within each decile is plotted. Negative values of ΔScr/Δt_wait correspond to improved renal function, while positive values of ΔScr/Δt_wait correspond to worsened renal function. The inverse relationship between degree of renal functional improvement and risk for AKI was statistically significant (p=0.008)."

(2) The findings that the absolute level of renal function pre-OLT was not a risk factor for AKI post-OLT and patients whose renal function declined while awaiting OLT were protected from AKI are surprising. Unfortunately, this data is between 16 and 20 years old. This important fact is missing from the abstract and should be included.

This information has now been added to the Abstract. The relevant sentence reads:

"To determine the impact of pre-OLT changes in renal function on AKI post-OLT, as well as to identify risk factors for AKI, we analyzed the prospectively maintained NIDDK Liver Transplantation Database, which includes patients who received their first OLT between April 15, 1990, and June 30, 1994."

(3) Currently, patients receiving OLT tend to have more severe hepatic and renal dysfunction and higher MELD scores than in the early 1990’s. In addition, there have been significant perioperative and intraoperative advances since these patients received their liver transplants. These differences limit the value of this study and the ability to apply the conclusions to the management of current day patients receiving OLT.

In this respect it is unusual that the authors do not indicate why it has taken so many years to analyze and present this information. There should be more discussion and explanation of the difference in eras.

We acknowledge the validity of the reviewer's comments. MELD score was included in the univariate analysis of co-morbidities, hepatic diagnoses, and complications (see Table 2), and was not significantly different between patients with and without AKI (15.8 ± 5.0 versus 15.7 ± 6.0, p=0.8).
We now discuss the differences between eras in a separate paragraph of our Discussion:

"Second, although we included MELD scores in our analysis, our patients came from the pre-MELD era, and risk factors for AKI may differ in the current era, in which patients undergo OLT with more severe renal function. In the last two decades, there have been medical and surgical advances in the management of patients undergoing OLT. These include caval sparing, split liver transplants, diminished use of veno-veno bypass, shorter anhepatic times, improved anesthetic techniques, and strategies to minimize calcineurin exposure. These improvements, while decreasing the risk for AKI during OLT, are counterbalanced by two factors, which simultaneously increase the risk for AKI: transplantation of patients with higher MELD scores, and expansion of the donor pool to include non-heart-beating and expanded-criteria donors."
Reviewer: Phuong Chi Pham

Major compulsory revisions:
(1) Renal function in the current study was measured by the MDRD estimated GFR. Any method of measuring renal function based on serum creatinine in cirrhotic patients has been well-documented to give an overestimate of true glomerular filtration rates. It must be cautioned that any study that is based on an inaccurate measurement of renal function may render any finding invalid.

This is a valid consideration. We now acknowledge this point in our Discussion. It is important to note, however, that we determined the correlation between development of AKI and changes in eGFR, rather than the absolute level of eGFR. The relevant text reads:

"Third, we used the MDRD formula to determine eGFR. Estimates of renal function in cirrhotic patients based on SCr are known to overestimate the true GFR. However, it is important to emphasize that our analysis was limited to the correlation between changes (not absolute levels) of eGFR and the development of AKI following OLT."

a. Urine output should have been included in the definition of post-operative AKI. This is especially important in patients with advanced liver disease because they are often overloaded and small fluctuations in serum creatinine may just reflect the extent of fluid administration.

Unfortunately data on urine output were available only for the intra-operative period. This limitation is acknowledged in our Methods in the following sentence:

"We did not use urine output in defining AKI because of the unavailability of these data."

b. The changes in urine output and net fluid balance during the pre-operative period over which the authors determined pre-operative renal function improvement or deterioration would have added valuable supporting evidence for the claim of either renal function improvement or deterioration. Improved renal function can lead to a diuretic phase and an initial transient small increase in serum creatinine. An increase in serum creatinine alone therefore does not necessarily imply worsening renal function of "AKI" in these patients.

We agree with the reviewer, and we have tried to present a balanced interpretation of our data. Ultimately, as concluded in the last paragraph of the Discussion:

"... there is a need for additional studies, which should include an analysis of peri-OLT kidney biopsies."
To emphasize the importance of this issue, as raised by reviewer, we have added the following paragraph to the Discussion:

"Although data on urine output were not available for the pre- and post-OLT periods, AKI and NO AKI patients did not differ in weight change from immediately before OLT to either post-OLT day 1 (1.2 ± 37.0 kg versus 1.2 ± 33.0 kg, p=0.995) or post OLT day 3 (–0.2 ± 37.0 kg versus –1.4 ± 35.0 kg, p=0.70). These data lend support to the notion that the observed differences in renal outcome post-OLT in AKI versus NO AKI patients cannot be attributed to differential changes in peri-operative volume status or extent of fluid administration. Moreover, as discussed above, AKI patients on average sustained a weight loss of ~14 kg while awaiting OLT. Such a weight loss would tend, if anything, to increase the concentration of SCr. Indeed, it is noteworthy that SCr decreased despite such a large decrease of weight, of which much was likely achieved through fluid removal. Taken together, the observed pre-OLT decrease of SCr among AKI patients would seem to be independent of dilutional factors."

The absence of a difference in peri-operative weight change between AKI and NO AKI patients would tend to rule out concentration effects as the sole basis of their difference in SCr and AKI occurrence.

Also bearing on this issue, is the course of AKI patients, of whom ~1/3 still fulfilled the AKIN criteria on post-OLT day 7. These data, as requested by the reviewer, are provided in point #4 below.

2. Exclusion of patients who required renal replacement therapy within the first day post-OLT. These patients could be in the “declining renal function prior to OLT” group who had worse renal outcome post-OLT. Exclusion of these patients may be a problem in the current study.

This is a valid consideration. We have analyzed our data to include the 11 patients who received dialysis on the first day post-OLT. Inclusion of these patients did not significantly change the association between declining renal function and decreased risk of developing AKI. These new data are given in Table S4, and are discussed in the Results:

"Finally, we repeated our analysis including the 11 patients who required dialysis on the first day post-OLT. Although these patients were excluded because the onset of their AKI was felt to precede the peri-OLT period, it is possible their exclusion may have led to under-representation in our analysis of patients whose renal function declined while awaiting OLT. Inclusion of these patients did not significantly affect the results of our analysis (see Table S4 in the Appendix). A significant correlation still existed between the development of AKI and the following pre-OLT renal functional variables: decreased ΔSCr and %ΔSCr; decreased ΔeGFR and %ΔeGFR; decreased ΔSCr/Δt and ΔeGFR/Δt."
3. Volume overload is a major problem in patients with advanced liver disease. It is not uncommon for physicians to administer excessive fluids to these patients when their renal function deteriorates. A fall in serum creatinine in these patients may therefore not necessarily reflect an improvement in renal function, but a dilutional serum creatinine level. In the current study, patients in the AKI group who reportedly had “improved renal function” prior to their OLT also had higher BMI. Could the higher BMI reflect higher volume overload status?

This is valid concern. While we cannot absolutely exclude this possibility, patients who developed AKI lost, rather than gained, weight while awaiting OLT, which if anything would tend to raise their SCr. We have addressed this issue in our Discussion. The relevant text is:

"Finally, consideration should be given to the possibility that a larger BMI reflects volume overload and profound ascites, with the observed decline of SCr in AKI patients being dilutional rather than indicative of improved renal function. However, as discussed above, this is unlikely, since these patients lost, rather than gained, considerable weight while awaiting OLT.

We have also greatly expanded our discussion of potential interpretations for the observed pre-OLT decrease of SCr among patients developing AKI. The revised text reads:

"Several potential explanations may account for the apparent protective effect of pre-OLT renal functional impairment on the development of AKI post-OLT. First, AKI in these patients may have been masked by an improvement in renal perfusion, leading to increased eGFR and decreased SCr. Because OLT reverses many circulatory abnormalities associated with decreased renal perfusion [19], patients often recover renal function post-OLT. It is estimated that a majority of patients awaiting OLT have some form of reversible renal dysfunction due to diminished renal perfusion.[20-23] Thus, in our study, it is possible that pre-OLT declines in renal function were reflective of changes in renal perfusion rather than intrinsic injury or loss of renal mass. OLT, by improving renal perfusion and inducing a decline in SCr and rise in eGFR, could mask small deteriorations in renal function consistent with milder stages of AKI. In accord with this possibility is the fact that a decline of renal function was a more powerful predictor for AKI-2/3 than for AKI-1 (see Tables S1, S2, and S3 in the Appendix).

Second, consideration should be given to the possibility that the pre-OLT decline in SCr among patients developing AKI is dilutional rather than indicative of improved renal function. While we cannot formally exclude this possibility, it is noteworthy that AKI patients sustained a loss, rather than gain, of weight (14.5 ± 32.0 kg) from registration until OLT, making it extremely unlikely that their decline of SCr can be attributed to dilutional effects. Third, the pre-OLT decline in SCr may reflect a loss of lean body mass, and it is the debilitation resulting from such a loss of body mass that predisposes to the development of AKI. Finally, pre-operative declines of renal dysfunction may truly protect patients from AKI, perhaps via ischemic preconditioning, as previously described for liver, kidney, and heart.[24-26]"
How was BMI calculated in these patients? Did body weights include ascites weight?

These issues are now clarified in the Methods. The relevant sentence is:

"Body mass index was calculated at the time of registration using actual body weight, including ascites."

Is it possible that the post-OLT AKI patients required and received higher IV fluids administration during the pre-OLT period because their hemodynamic parameters were consistent with worse circulatory failure (higher CO, lower SVR) compared to their “no AKI” counterpart. Their ”improved renal function” pre-OLT could have just reflected a dilutional creatinine level.

The possibility that improved renal function pre-OLT in AKI patients reflects a dilutional effect is discussed above. As noted, AKI patients lost rather than gained weight, making a dilutional decrease of SCr unlikely. The relevant text from the Discussion is:

"Second, consideration should be given to the possibility that the pre-OLT decline in SCr among patients developing AKI is dilutional rather than indicative of improved renal function. While we cannot formally exclude this possibility, it is noteworthy that AKI patients sustained a loss, rather than gain, of weight (14.5 ± 32.0 kg) from registration until OLT, making it extremely unlikely that their decline of SCr can be attributed to dilutional effects."

4. Duration of follow-up: a 7-14 day follow-up in both AKI and no AKI groups would be helpful to determine if the post-OLT AKI during the first 48 hours was indeed clinically significant or just a reflection of transient changes in fluid and hemodynamic status.

Follow-up data at 7 days for both AKI and NO AKI patients are now provided in the results. As noted, the etiology and risk factors for AKI developing >2 days post-OLT are likely distinct from those for AKI in the immediate period post-OLT. The relevant text from the Results is:

"We examined the outcome of AKI and NO AKI patients at 7 days post-OLT. Of the 243 patients who developed AKI within 2 days of OLT, 3 died, 160 recovered, and 80 still suffered from AKI (53 AKI-1, 3 AKI-2, and 24 AKI-3). Eight patients received RRT. Of the 445 patients without AKI in the first 2 days post-OLT, 4 died and 291 subsequently developed AKI (77 AKI-1, 13 AKI-2, 60 AKI-3), with 25 requiring RRT. The etiology and risk factors for AKI developing >2 days post-OLT are likely distinct from those for AKI in the immediate period post-OLT."