Dear Drs. Akbulut, Mehta, Papalois, and Salvadori

I thank World Journal of Transplantation's team/reviewers for their input on the manuscript titled "Kidney Disease in Non-Kidney Solid Organ Transplantation." I have addressed individual comments below.

Reviewer: 1

Comments to the Author

Undoubtedly, chronic kidney disease is an extremely important clinical issue in organ transplant patients. The author undertook the difficult task of reviewing the literature, for which he should be congratulated. However, several important shortcomings should be mentioned:

Comment 1.1: Author doesn't provide accurate numbers when quoting other authors - i.e. "non-CNI related causes of kidney disease have been implicated at rates between 27-40% in solid organ transplant recipients who have undergone kidney biopsies". Such numbers don't appear in the original article.

Response 1.1. Thank you for your thorough, insightful review. This number was derived from Figure 1A and 1B as presented in the study by Ojo: Ojo AO. Renal disease in recipients of nonrenal solid organ transplantation. Semin Nephrol. 2007 Jul;27(4):498-507. doi: 10.1016/j.semnephrol.2007.03.010. PMID: 17616280.

Figure 1A denotes that in orthotopic heart recipients with ESRD (n=24), 40% had evidence of non-CNI related pathology on biopsy. Similarly Figure 1B describes a rate of 27-28% of non-CNI pathology on kidney biopsies in liver transplant recipients.

I have updated the manuscript to acknowledge how I obtained this number and caveats below:

"Non-CNI related pathology, as illustrated in their description of orthotopic heart and liver transplant recipients in their cited figures, is also an important player and has been observed in 27-40% of kidney biopsies. Importantly, histologic findings must be interpreted cautiously as these biopsies were subject to having multiple concurrent histologic patterns. (10)"

Comment 1.2: The author also doesn't mention the fact that CNI related causes of nephrotoxicity in the same work accounted for 46-60% of cases and constituted the largest group of reported histologic lesions.

Response 1.2: Thank you for pointing this out. I have updated the manuscript accordingly:

"In a recent study, Ojo noted that CNI use constitutes the majority of histologic lesions observed on kidney biopsy, ranging from between 46-60% of cases."

Comment 1.3: Organ specific paragraphs constitute of chaotic presentation of random manuscripts providing a compilation of abstracts with no clear clinical application in mind.

Response 1.3: Thank you for this comment. I chose to organize kidney disease in non-renal solid organ transplant by transplanted organs to highlight unique causes/contributors to kidney disease in addition to shared mechanisms. I thought it afforded an opportunity to provide some background of kidney disease in said organ, describe unique factors that portend chronic kidney disease, and then summarize these findings in hopes of providing a clear clinical application, when possible.

Furthermore, the section "Diagnosis and Management of Chronic Kidney Disease Post Non-Renal Solid Organ Transplant" was intended to provide clear clinical application.

I have added summarizing paragraphs to the end of the kidney disease after lung transplantation and kidney disease after intestinal transplantation sections as observed below:

KIDNEY DISEASE AFTER LUNG TRANSPLANTATION

"Kidney disease, both in terms of AKI and CKD, is common in lung transplant recipients. There appear to be certain risk factors associated with CKD development, namely lower pre- and early post-transplant creatinine, AKI, end stage lung disease from CF, and older recipient age. There appears to be a subset of lung transplant recipients at higher risk for progressive CKD. Early transplant nephrology referral may be of benefit for these patients. Despite CKD commonly manifesting post-lung transplant, modifiable/preventable risk factors including diastolic blood pressure and CMV infection are potential targets in terms of blood pressure optimization and prophylaxis strategies to mitigate CKD development.

In summary, early multidisciplinary care and co-management from transplant pulmonology and nephrology is vital for appropriate patient selection and continued management of kidney disease in lung transplant recipients."

KIDNEY DISEASE AFTER INTESTINAL TRANSPLANTATION

"Kidney disease after intestinal transplant is understudied. Even so, there are key takeaways that can be derived from the data to date. In this moribund population, perhaps measured GFR and/or cystatin C could be used adjunctively with typical estimating equations to better characterize kidney function and guide nephrology referral/management. One can surmise that a subset of patients i.e. older, diabetic intestinal transplant recipients, with persistent IV fluid needs could benefit from early transplant nephrology care."

I also made acknowledgement to the excellent study by Wiseman which describes in detail nephrology referral and management considerations throughout SOT in the following section:

Nephrology referral/management considerations

"The integration of nephrology care into dedicated NKSOT care throughout various stages of pre-,peri-, and post-transplantation is critical for diagnosis and management of kidney disease. Wiseman, in his recent review, provides substantive recommendations on timing/appropriateness of nephrology referral, based on KDIGO guidelines, and management considerations across transplant timepoints in tabular form. (13)"

Comment 1.4: Despite a vast amount of available data on CNI minimalization strategies, the author does not provide a reliable and clinically useful review.

Response 1.4: Thank you for this insight. I have expounded on this in the subsection *Calcineurin inhibitor use/minimization strategies* in the section **DIAGNOSIS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE POST NON-RENAL SOLID ORGAN TRANSPLANT** as shown below:

Calcineurin inhibitor use/minimization strategies

"With CNIs as possible potentiators of CKD, CNI-sparing/minimizing maintenance immunosuppression regimens have been proposed as a renoprotective management strategy. There is a large body of evidence examining CNI minimization in NKSOT, which we will discuss below.

With the advent of tacrolimus and results of ELITE-SYMPHONY, tacrolimus has ousted cyclosporine CNI-wise, as tacrolimus appears to have a less nephrotoxic profile. (55) Mechanistically, this may be due to less renal vasoconstriction as has been demonstrated in both *in vivo* and *in vitro* studies (3, 56, 57).

Pancreas transplant wise, limited evidence exists supporting CNI minimization or sparing. While Kandula et al. compared tacrolimus-sirolimus based regimen to tacrolimus-mycophenolate immunosuppression in pancreas transplant alone recipients, mean tacrolimus levels were similar across groups at all time points. (58)

In the context of liver transplantation, there is an expansive body of literature supporting the use of CNI-sparing or minimization therapy with sirolimus (59-61) and mycophenolate (62-64).

For heart transplant recipients, CNI minimization/sparing has been shown as a viable immunosuppression approach. Cornu et al. in their systematic review and meta-analysis of eight studies on CNI minimization showed that creatinine clearance was preserved in individuals with impaired renal function, which they defined as eGFR <60ml/min, at 6 months [+12.23 (+5.26, +18.82) ml min−1, P = 0.0003). Although longer term benefit was not shown in this study, CNI minimization strategies were not associated with increased rejection, mortality or adverse events compared to the standard CNI regimen approach (all P >0.05). As is aptly described by Zuckermann et al., the use of induction in OHT recipients has "provided immunosuppressive cover" to allow for the following approaches: CNI minimization and delayed CNI introduction whilst kidney function is recovering post- heart transplantation. (65-69)

In lung transplant recipients, evidence exists supporting the use of CNI sparing/minimization regimens. Chandrashekaran et al. in their recent review describe a following approaches including basiliximab induction, which showed favorable short

term renal outcomes. (70) They also noted CNI minimization approaches with tacrolimus/mammalian target of rapamycin (mTOR) inhibitor combinations which showed improved renal function with comparable allograft/patient survival. Notably, mTOR use was associated with increased wound complications, proteinuria, hypertension, post-transplant diabetes and dyslipidemia. They also highlighted CNI minimization approaches with mTOR use instead of anti-metabolite immunosuppression. Strueber et al. examined 190 lung transplant recipients randomized to everolimus or mycophenolate mofetil (MMF) 1 month post-transplant. Though results limited due to lack of completion of the study protocol, rejection and infectious complications were lower in the everolimus group of whom 20-28% of recipients were also on reduced CNI doses. (71) In a 3-year multicenter randomized prospective study, Glanville et al. did not show significant differences in creatinine at 3 years comparing lung transplant recipients on mycophenolate sodium versus everolimus. While the authors stated that they utilized reduced 2-hour post-dose CSA levels in the everolimus group and that "most levels measured were within pre-specified target ranges", granular data describing CNI levels in these cohorts is lacking. (72) Further in support of CNI minimization/sparing is a study by Stephany et al., who observed improved GFR durable out to 18 months for lung transplant recipients converted to sirolimus-based immunosuppression, with the greatest benefit incurred to lung transplant recipients without proteinuria. (73)

In IT recipients, the benefit of CNI minimization/sparing strategies appears to be limited in terms of preserving renal function. Rutter et al. in their single center study demonstrated significant decline in renal function irrespective of tacrolimus exposure. (74) Herlenius et al., in their study of 10 IT recipients, noted that 4 patients were switched from CNI to sirolimus based regimen. (75) Of these, one developed renal failure leading to hemodialysis, one died due to hemorrhage with CKD IV at the time of death, and the other 2 had "stable GFR" at 2 and 3 years post conversion without developing rejection or intestinal allograft failure.

Based on the initial successes of the BENEFIT and BENEFIT-EXT trials comparing belatacept to cyclosporine in kidney transplant recipients, belatacept in lieu of CNI or with CNI minimization has been proposed as a novel immunosuppression strategy for NKSOT. (76, 77) There is mounting research describing CNI-minimizing or sparing approaches using belatacept in OHT recipients (78), lung transplant recipients (79), and PTA recipients. (80, 81). More robust studies e.g. randomized control trials with longer follow-up are needed to better understand outcomes related to belatacept in NKSOT as these early studies are limited in design (case-series, retrospective studies) and follow up.

An important caveat to belatacept use is that of liver transplantation. As demonstrated by Klintmalm et al. in their phase II trial and Schwarz and colleagues, concerns exist regarding allograft function and safety with belatacept. (82, 83) Though results from a

study conducted by LaMattina were more favorable, these are limited due to small numbers as well as the patients being converted back to a CNI-based regimen. Thus, belatacept use in liver transplantation is at most controversial. Additional studies sufficiently powered are needed to determine efficacy and safety of belatacept in liver transplant recipients.

Approaches to minimize CNI use via induction/maintenance immunosuppression appear promising in terms of preserving renal function. While these often incur adverse effects related to specific therapies e.g. mTOR inhibitors, in several instances, they have not lead to decreased allograft or patient survival. Appropriate, sufficient CNI minimizing immunosuppression tailored to preserve renal function while also staving off rejection is achievable via multidisciplinary collaboration and dialogue between transplant experts across nonrenal organ systems and transplant nephrology."

Comment 1.5: Moreover the suggestion that the use of belatacept is a safe immunosuppressive strategy in liver transplant patients is at most controversial. A single quoted manuscript by LaMattina constituted of a small group of patients which were subsequently converted to CNI. Most of betalacept studies in liver transplantation show higher incidence of rejections rates, death and PTLD (particulary in EBV "-" patients). With the available data the use of belatacept cannot be recommended in liver transplant recipients. Additional studies with sufficient power are needed to determine efficacy of belatacept in the liver transplant population.

Response 1.5: Thank you for pointing out this oversight. I have elaborated on this in the subsection *Calcineurin inhibitor use* in the section **DIAGNOSIS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE POST NON-RENAL SOLID ORGAN TRANSPLANT** as shown below:

"Based on the initial successes of the BENEFIT and BENEFIT-EXT trials comparing belatacept to cyclosporine in kidney transplant recipients, belatacept in lieu of CNI or with CNI minimization has been proposed as a novel immunosuppression strategy for NKSOT. (76, 77) There is mounting research describing CNI-minimizing or sparing approaches using belatacept in OHT recipients (78), lung transplant recipients (79), and PTA recipients. (80, 81). More robust studies e.g. randomized control trials with longer follow-up are needed to better understand outcomes related to belatacept in NKSOT as these early studies are limited in design (case-series, retrospective studies) and follow up.

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belatacept use in liver transplantation is at most controversial. Additional studies sufficiently powered are needed to determine efficacy and safety of belatacept in liver transplant recipients."

Comment 1.6: While I appreciate the considerable amount of work that went into preparing the manuscript, it is extremely difficult for me to recommend this review as clinically valuable.

Response 1.6: Thank you for this comment. I hope that my revisions will suffice in improving this manuscript.

Reviewer 2:

Comment 2.1: Interesting article on kidney disease in patients with nonrenal transplantation with comprehensive overview. Great work!

Response 2.1: Thank you for reviewing this manuscript and for your comment.

Reviewer 3:

Comment 3.1: The manuscript entitled "Kidney Disease in Non-Renal Solid Organ Transplantation Population: A Review" prepared by K.J. Swanson provides data regarding the current literature about kidney disease in non-kidney solid organ transplantation. The manuscript is organised into several sections in which the author point out the most relevant data regarding kidney diseases after pancreas, lung, liver, heart and intestinal transplantation.

Response 3.1: Thank you for your excellent review of this manuscript.

Comment 3.2 To improve the manuscript, we recommend/Major points: 1. In the materials and methods section, an expansion of the data presented or a figure related to the research process conducted in the different databases could be a good factor to highlight the information presented.

Response 3.2 Thank you for this feedback. I have included key words utilizing in our search to the materials and methods section as below:

We conducted literature searches in PubMed, EMBASE, Cochrane, CINAHL (Cumulative Index to Nursing and Allied Health Literature) from database inception to January 2022, as well as Google Scholar and reference lists of relevant studies and reviews. Key words utilized in our search included the following: "Chronic kidney disease; native kidney function; non-renal solid organ transplant; non-kidney solid organ transplant; acute kidney injury; calcineurin inhibitor; calcineurin inhibitor nephrotoxicity; renal replacement therapy; kidney failure; hemodialysis; pancreas transplant alone; lung transplant; liver transplant; heart transplant; intestinal transplant;

mTOR inhibitor; belatacept; CNI-minimization; immunosuppression; proteinuria; albuminuria”

We limited our search to studies with available full text and English language.

Comment 3.3 The tables should be associated with legends.

Response 3.3 Thank you for noting this. I have updated the tables with titles describing them as well as legends with abbreviations and definitions.

Comment 3.4 In the sentence "While quantifying the prevalence of CKD in any population is a daunting task, several studies have noted an incidence of CKD in non-kidney solid organ transplant ranging between 6-21%" the author should add a reference related to the data presented.

Response 3.4 Thank you for informing me of this oversight. I have added citations appropriately as demonstrated below:

“While quantifying the prevalence of CKD in any population is a daunting task, several studies have noted an incidence of CKD in non-kidney solid organ transplant ranging between 6-21%. (2, 3)”

Re-reviewer:

Comments: Thank you for the revision. The overall quality of the manuscript has increased.

Response: Thanks for your comments.

Thank you

Kurtis J. Swanson MD