

Manuscript NO: 49627

Title: Common histopathological characteristics and causes of graft failure in the current era of immunosuppression among kidney transplantation recipients: a Single-center experience

Dear Editor and reviewers,

Thank you for the careful review of our manuscript. As a result of your thoughtful comments and critique, the quality of the paper has improved significantly. Please find our point-by-point response below.

SPECIFIC COMMENTS TO AUTHORS

Comments to Common histopathological characteristics and causes of graft failure in the current era of immunosuppression among kidney transplantation recipients

Introduction section Well written, concise and clear.

--Thank you

Methods Immunosuppression subsection: Do UW protocols consider calcineurin inhibitor (CNI) (tacrolimus) dose reduction in failing grafts? Or even tacrolimus replacing by mTOR inhibitors? As the studied cohort is contemporaneous with the concept of CNI nephrotoxicity it could be interesting to mention that issue.

--At UW we do not routinely reduce CNI on failing graft unless there are features of CNI toxicity on biopsy. But once graft fails, we slowly taper immunosuppressive medication and maintain on low dose prednisone only. mTOR inhibitors are not commonly used at our University and rarely on failing grafts. We have recently started using co-stimulatory blockade with belatacept in selected few cases mainly on provider discretion. This has been added in the "Immunosuppressive" section.

Kidney allograft subsection: Are protocol biopsies reported from all those patients with pre-transplant DSA in the result section or this issue is a mere description of the UW protocol? I ask because, I think not all patients having DSA and who received a graft did bad and these number could bias the results.

--Protocol biopsy is just a description of our protocol. As explained, in that section we do

not routinely perform protocol biopsy and most of the biopsies in this study were for the cause- mainly for an unexplained rise in serum creatinine or proteinuria.

Please, clarify. Results Biopsy findings and common causes of graft failure subsections are misleading. Both show histopathological findings from the same tissue samples, but the data interpretation suggests that even IFTA is more frequent than AR, AR is the leading cause of graft failure. How do authors reach to this conclusion?

--Sorry for the confusion, as you know there could be multiple findings on the same biopsy. For the cause of graft failure- we included the first (primary diagnosis). This was explained in the "Data Collection" section as "In cases where a patient had multiple biopsy diagnoses, all diagnoses were also reported separately, although the primary diagnosis (first diagnosis) was used for the cause of graft failure."

Common causes of graft failure based in the cause of ESRD subsection and Table 2: What is the meaning of "p for trend" in Table 2? It is not clear that a "trend" does exist between three discrete diseases.

--Thank you, as there were more than two comparison groups, GN, DM, and HTN- so the cause of graft failure and statistical analysis were presented as a trend among these three variables. We have removed the p-trend column from table 2.

Causes of graft failure according to time post transplantation subsection: "Acute rejection, mainly ABMR, was the most common cause of graft failure", please show the respective figures for ABMR, ACR and mixed rejections. In a previous subsection and Figure 3 it is stated that "acute rejection.... 40% (32% ABMR or mixed rejection and 8% ACR)", but, the same could be written in a different way: x% ABMR, y% ACR and z% mixed rejections. All graft rejections are immune mediated, but, the histological analysis could show more or less ABMR or ACR findings that not necessarily preclude the existence of one or the other type of immune mediated damage to the graft.

--Thank you for this interesting point, 23% of early graft failures were due to ABMR or mixed rejection and 8% were due to ACR and has been added in the respective section.

Discussion First paragraph, please consider the above comments about the types of rejection.

--The second sentence (first paragraph) of the section "Discussion" comments about rejection is the most common cause of graft failure and particularly ABMR.

Please comment about the almost inexistent calcineurin inhibitor related toxicity as a culprit of graft failure in the analyzed biopsies, once considered a main etiology of IFTA and a suspicious etiology of ABMR after transplant physicians decreased the immunosuppressive intensity after the first-year post transplantation.

--Thank you for this interesting point. We have added a sentence about CNI toxicity not being a common cause of graft failure in our cohort in the first paragraph of the "Discussion" section.

References, Tables and Figures OK (please review "p for trend" in Table 2. Abstract OK.

--Thank you, as above we have removed the p for trend from Table 2.