Author’s response to reviews

Title: Outcomes for kidney transplant recipients admitted to the intensive care unit: a retrospective study of 200 patients

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Author’s response to reviews:

Dear Prof. Dusse,

Thank you very much for sending out for review our study entitled: “Outcomes of kidney transplant recipients admitted to the intensive care unit: a retrospective study of 200 patients”. Your comments, and the comments of the reviewers were helpful and will increase the validity of the study and of the observations.

As you can see below in a point-by-point response letter, we positively answered all the inquiries.

Looking forward to your decision,

Sincerely yours,
Editor Comments

Comment 1: A legend for fig. 3C is missing / the sub-numbering for fig. 3 is confusing

Answer 1: In the revised version, Figure 3 and legends were modified, as appropriate.

Reviewer 1

Comment 1: There are some grammatical and typographical errors somewhere in the article that needs to be considered by an expert editor. In abstract the [EBV] is abbreviated without describing its whole name.

Answer 1: As suggested, the manuscript was corrected by a native English speaker. The term EBV was also replaced by Epstein Barr virus.

C2: The primary and secondary objectives were : The primary objective of the study was to identify the predictive factors of death in the hospital of KTR admitted to the ICU. Secondary objectives were the characterization of the risk to develop AKI to CKD transition and to acquire HLA immunization). But in the conclusion of the "abstract" they did not address them appropriately. Conclusion should be concise and only related to what they found.

A2: As suggested, conclusion of the abstract was modified, as appropriate.

C3: In the body of manuscript, the large-scale data presented are valuable to read but it is better to concentrate on what they defined as primary and secondary outcomes because a reader would be confused of reading too much data. Considering the above-mentioned corrections, the MS values to be published.

A3: As suggested, primary and secondary objectives were more emphasized in the Result section.

Reviewer 2: This manuscript potentially adds to the literature on the course and outcome of kidney transplant recipients (KTR) after requiring therapy on an intensive care unit (ICU).
While the study is a single institution retrospective observational cohort study, it is including a high number of KTRs admitted to an intensive care unit (ICU) (n=200). It also provides relevant information on rate, timing and causes of ICU admissions in a large cohort of KTRs (n=1240) (*). In addition, the study shows in hospital mortality and survival in KTRs admitted to the intensive care unit and aims to evaluate its predictive factors (**). Furthermore, the authors aim to specify the risk factors of progression from acute kidney injury (AKI) to chronic kidney disease (CKD) (***) and anti-HLA immunization in this scenario (****).

Comment 1: The article provides valuable information, given that, compared to other studies (also cited in this article, e.g. 1, 2 and 5) the analyzed cohort is substantially larger and well characterized in its course before ICU admission (Table 1). The study showed, within the large investigated cohort (n=1240), an ICU admissions rate of 7.7%, which was in line with previous studies (cited in this article, e.g. 1, 2 and 5), and is therefore investigating an important frequent scenario in the course after transplantation. As authors identify, in line with other studies, sepsis and ARF are main causes of ICU admission in KTR. But still, ICU admission had multiple causes. For example, almost ¼ of the patients were admitted within the postoperative period (peritonitis, hemorrhage, 23%). Different causes of admission, requiring substantial different management and treatment on the ICU. This makes the investigated cohort highly heterogeneous, a fact that needs to be in mind for all further conclusions.

Answer 1: As suggested by the reviewer, we reinforce this part of the study limitations (Discussion section; page 14)

C2: We agree that the data on EBV viremia and BK viruria before ICU admission and its association with poorer outcomes are of special interest. Viral replication is a known marker for over immunosuppression and over immunosuppression increases the risk of infection. The authors also state, over 50% of ICU admissions were related to infections. Therefore including, if available, immunosuppression dosing and blood levels before ICU admission in the analysis would be of interest.

A2: As suggested, calcineurin inhibitors blood levels before ICU admission were added to the manuscript (Results section).

C3: The authors showed, that progression of CKD after ICU admission highly prevalent (45% at 6 month). We think to identify KTRs that progress to CKD is in general of great importance, showing the group of KTRs admitted to an intensive care unit is of special interest.

A3: As suggested, the characteristics of the KTRs that progress to CKD was given in supplementary figure 1.

C4: In general, developing anti-HLA DSAs and its impact on the allograft is of great importance. The authors provide important data on anti-HLA immunization. However, data on anti-HLA
antibodies were available only in about half of the investigated cohort and in terms of reason for ICU admission the investigated cohort was highly heterogeneous.

A4: Here, we characterize the risk of HLA immunization at month 6. At that time, 50 patients (30%) were died. HLA immunization (obtained between month 4 and 6) was thus investigated in 112/150 patients (75%). As suggested, heterogeneity was discussed at the end of the Discussion section (see comment 1).

C5: Page 4, line 4,5: "Thus, there is an unmet need to better characterize the survival of KTR admitted to the ICU, but the renal and immunological outcomes of survivors."

Unclear meaning, needs clarification.

A5: As recommended, the manuscript was revised by an English native speaker.

C6: Page 11, section "immunological outcomes": A reference of Figure 3 C is missing within the section and within the article.

A6: As recommended, Figure 3 and references were changed, as appropriate.

C7: Page 11, line 26,27,28: "Patients that did not acquire HLA immunization during ICU had a significantly poorer renal prognosis (62 vs. 90% functional graft at 12 months; p=0.06)": Is this statement in line with figure 3 C, and if yes, because the authors analyze a subgroup, it needs clarification.

A7: This statement is not in line with figure 3C. It only concerns the sub-group of patients with immunological data available at M0 and M6 (n=112). As said in comment 6, Figure 3 was modified and references were changed, as appropriate.