Conflict of interest

The authors declare no conflicts of interest.

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Response to Invited Commentary "Undoubtedly, kidney transplant recipients have a higher mortality due to COVID-19 disease compared to the general population"

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This is a Response to Forum: Bilgin Osmanodja, Manuel Mayrdorfer, Fabian Halleck, Mira Choi & Klemens Budde. Undoubtedly, kidney transplant recipients have a higher mortality due to COVID-19 disease compared to the general population. Transplant International 2021:34; 769

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We appreciate the opportunity to have this scientific discussion regarding the important question, whether

organ transplantation is an independent risk factor for COVID-19-related death.

We completely agree with the statement by Budde *et al.* that "... kidney transplant recipients have a higher mortality due to COVID-19 disease compared to the general population."

We agree with Budde *et al.* that the title of our article could be misinterpreted and could be concretized as follows: "Solid Organ Transplantation is not an independent risk factor for COVID-19 disease outcome."

The aim of our analyses was to identify the risk for a fatal outcome in transplanted and SARS-CoV-2-infected patients in comparison with SARS-CoV-2-infected patients who have not received a transplant. Therefore, our target population of cases and controls was defined as SARS-CoV-2-infected in- and outpatients in Germany. In order to minimize recruitment bias, it was important that controls were recruited in the same period of time as the cases. Therefore, the cases and controls were selected from LEOSS, representing the largest cohort of SARS-CoV-2-infected patients in Germany. Consequently, we do not agree with Budde and colleagues that the general population would be the appropriate control group for our research question.

Our study population was matched by age, gender, and comorbidities, with matching for comorbidity given a priority over age. The reported finding was stable over multiple iterations of different matching strategies, and we stay with our statement that our analysis did not show an additional risk for severe courses of disease by the transplantation itself.

Patients after transplantation are not as healthy as the "general population" but rather have multiple comorbidities as can be easily appreciated in the table provided by Budde *et al.* in his response to our article published in TI. For example, in the publication by Akalin and colleagues, incidence of hypertension was 94%, diabetes almost 70%, heart disease 17%, or lung disease 11%. These comorbidity frequencies in the transplant population are far beyond frequencies in the general population and may be well responsible for the increased mortality of transplant recipients compared to general population. In this context, we also completely agree that organ transplant recipients should be highly prioritized for SARS-CoV-2 vaccination.

Nevertheless, this was not our scientific question. The question of our study was whether prior receipt of a solid organ transplantation, always connected with immunosuppressive therapy, was associated with increased mortality of COVID-19 patients. The results we gained indicated that neither immunosuppressive therapy nor organ transplantation itself remained independent risk factors for COVID-19-related death, when adjusting for potential confounders and after comorbidities were matched with COVID-19 patients who are not transplanted. We find these results highly relevant and important, especially considering triage decision-making during the early phase of the pandemic in some areas and circumstances.

In this context, in many countries mortality rates in transplant recipients were increased two- to threefold when cases infected before April 2020 (peak of first pandemic wave) were compared with cases after April 2020 (unpublished results). This important point can also be appreciated in the table provided by Budde *et al.* and points toward a possible selection/treatment bias by first wave studies in certain countries/areas, where triage decisions may have had an additional influence.

While last patient data for this manuscript have been collected in May 2020, including patients from the Charité hospital, the German healthcare system during this first pandemic wave in spring 2020 was not at all overstressed/challenged by COVID-19 patients making selective triage decisions for transplant recipients highly unlikely [1].

We also do not agree that the results are because of an obvious selection bias. Not only the control group as stated by Budde et al. but both transplant and control patients were selected from the Lean European open Survey on SARS-CoV-2-infected patients (LEOSS), the largest COVID-19 register in Germany, including hospitalized and nonhospitalized patients. Therefore, LEOSS can be described as a highly representative cohort because of its anonymized and trans-sectoral recruitment strategy. We actually view this as an important strength of our study that all patients were selected from the same registry indicating that in principle the same referral centers provided data for all COVID-19 cases examined in our letter.

The major limitation of our study as pointed out in the letter is the limited number of cases. Hereby, deviations by chance cannot be excluded. We also agree that, because of comorbidity matching, age matching appeared suboptimal. Nevertheless, during the review process, we also checked our study data at the level of 62 transplant recipients with markedly improved age

matching and confirmed our results as published. Because of space restrictions, this information was not included in the original letter. In addition, our data are consistent with other publications, for example with the work by Molnar and coworkers [2], in which a registry of more than 4000 intensive care patients with COVID-19 disease was used to ask the equivalent question as we did and where ICU-treated organ transplant recipients were matched with other ICU patients demonstrating equivalent mortality rates independent on organ transplantation.

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Did an effect of kidney transplantation on COVID-19 mortality go unnoticed due to selection bias?

Thomas Neyens

This Forum discusses Letter by Hugo et al: Solid organ transplantation is not a risk factor for COVID-19 disease outcome. Transpl Int. 2021:34; 378.

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I have read the letter by Hugo *et al.* [1] and the commentary with interest. Hugo *et al.* [1] conclude that they could not show adverse effects of prior solid organ transplantation on COVID-19 mortality, based on a case-control analysis. The commenters claim that this conclusion is incorrect, due to selection bias in the case-control matching. I acknowledge the good scientific intentions of all authors involved; in what is written below, I will share my insights, form a statistical point of view, without expert knowledge of transplantation science and the related literature.

The research question in the letter by Hugo *et al.* [1] is clear: 'Is solid organ transplantation history associated with mortality in COVID-19 patients?'. The study adopts an observational, retrospective design. To the best of my understanding, the data in the sample were collected in a non-probabilistic way, that is there was no process to choose participants before the data were collected in function of the research question at hand. Instead, the researchers use a database that contains a subset of the COVID-19 patient population. Probabilistic matching is then used to correct for baseline differences between cases, that is COVID-19 patients with a transplantation history, and controls, that is COVID-19 patients without a transplantation history. The matching is important, since these differences might confound the association under investigation, namely the effect of transplantation history on COVID-19 mortality. The researchers match for age, gender and comorbidities. In other words, if matched correctly, they draw conclusions on differences in mortality between COVID-19 patients with and without a transplantation history who have similar characteristics in terms of gender, age and comorbidity distributions.