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## Is transplantation per se a risk factor for worse outcome of SARS-CoV-2 infection in kidney transplant recipients?

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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. and Forum by Budde K. Undoubtedly, kidney transplant recipients have a higher mortality due to COVID-19 disease compared to the general population. *Transpl Int* 2021. 34;769.

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We read with great interest the recent article by Hugo *et al.* reporting comparable mortality following SARS-CoV-2 infection in 46 solid organ transplant (SOT) recipients compared in multivariable conditional logistic regression to 1380 controls without transplantation matched for known COVID-19 risk factors [1], and the responding letter by Budde *et al.* suggesting misinterpretation of the data due to a selection bias of the control population [2]. The latter fear that misleading conclusions could have detrimental effects on decision making concerning risk-stratification and immunization strategies.

Since the beginning of the SARS-CoV-2 pandemic and through the different waves that hit our countries, overwhelmed healthcare systems with triage for access to life-saving ventilator support, different thresholds for intubation, evolving ventilation techniques including lung protective strategies, high-flow nasal cannula or non-invasive positive pressure ventilation [3], as well as multiple treatment strategies including hydroxychloroquine, azithromycin, lopinavir/ritonavir (mostly used during the first wave), and dexamethasone, remdesivir, tocilizumab, convalescent plasma (mostly during the second wave), altogether led to mortality rates that largely fluctuated, decreased for instance in Spain from 24% to 13.2% between the first and second wave [4], and largely limit comparisons between studies and populations. Except for dexamethasone, reports on favourable effects of the various used medications are scarce, most being without any notable beneficial effect [5]. Although specific risk factors for severe outcome; including age, body mass index, diabetes mellitus, pre-existing cardiopathy, chronic lung disease and basal renal function have been identified, it remains unclear how pre-existing SOT influences COVID-19 outcome [6, 7].

Whereas initial reports during the first wave from New York suggested increased mortality in SOT recipients with COVID-19 [8], a first experience from the Swiss Transplant Cohort Study (STCS) limited to 21

SOT recipients suggested the absence of higher rates of complications as compared to the general population [9]. It was hypothesized that immunosuppressive regimens of SOT recipients might be protective against the hyperinflammation responses contributing to ARDS development in COVID-19. Since then, several reports have presented conflicting results concerning the severity and mortality rates of SOT recipients with COVID-19 [10-14]. SOT recipients might not all be at the same risk for worse outcome, depending on the type of transplant and underlying diseases, belonging to the above cited and well-established risk factors [15]. Obviously, lung transplant recipients with pre-existing impaired and fragile lungs are potentially at higher risk for complications than other types of transplant recipients. In the same line, kidney transplant recipients (KTR) might also be at increased risk for complications due to their frequent underlying comorbidities including diabetes, hypertension, cardiovascular diseases and reduced renal function. Recently, Chavarot et al tried to decipher the influence of both immunosuppression and comorbidities on the outcome of KTR with COVID-19 using a propensity score matching [16]. Their study, including 83 KTRs

matched to 83 controls from non-transplanted patients comparable in terms of age, sex and comorbidities, suggested that kidney transplantation *per se* was not associated with a higher risk of complications or mortality, thereby supporting the observation by Hugo et al.

In the light of the limitations for study comparisons expressed above, how can we now integrate the results presented by Hugo et al. and the concerns of Budde et al.? At the time being, it seems reasonable to assume that kidney transplantation *per se* might not be associated with worse outcome, but that underlying comorbidities of kidney transplant recipients might influence the outcome similarly as in the general population. Therefore, kidney transplant recipients, as well as all other SOT recipients with comorbidities, should remain a priority population for immunization strategies. It remains also to be evaluated whether the risk of severe COVID-19 in patients dialysed while on the kidney transplant waiting list differs compared to the risk of those having received a kidney transplant, once matched for associated comorbidities (17).

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