

Mortality in solid organ transplant recipients with COVID-19: More than meets the eye

To the Editor:

We read with interest the study by Heldman and colleagues¹ showing that, similar to the trends observed in the general population, mortality in solid organ transplant (SOT) recipients with COVID-19 significantly declined over time. Within the limitations associated with the study's retrospective nature, this finding supports the concept that advances in care and COVID-19 therapies improved outcomes in SOT recipients.

The accompanying editorial of this article² questions whether mortality in SOT is, in fact, lower than in the general population. This is an intriguing question, based on the hypothesis that chronic immunosuppression limits the detrimental effects of the uncontrolled anti-SARS-CoV2 response, including "cytokine storm" and acute respiratory distress syndrome (ARDS). The authors of the editorial discuss data from small cohorts of SOT with COVID-19 or other infections to conclude that "SOT recipients are at increased risk for infections, but paradoxically are at similar or decreased risk for infection-related mortality compared to non-SOT patients".

In the absence of strong evidence from an ad hoc designed prospective study, we advise a more cautious interpretation. We contend that only cohort studies comprising all outpatient diagnoses can provide a fair comparison between SOT recipients and the general population. Outpatient diagnoses are needed to correctly count the denominator of both SOT recipients and the general population with COVID-19, to assess whether SOT are more likely to develop severe COVID-19 disease requiring hospitalization compared to the general population. For example, if 25% is the mortality among all hospitalized patients (SOT recipients and non-transplanted patients), but the risk of hospitalization is four times higher in SOT recipients compared to the non-transplanted patients, then the mortality would falsely appear equal between the two groups if only hospitalized patients were analyzed. In fact, the actual mortality would be four times higher in SOT recipients (Figure 1).

A large Italian study compared mortality from COVID-19 between 450 solid organ transplant recipients and 238 895 individuals from the general population, including both outpatients and inpatients. SOT recipients had worse survival, with the adjusted odds of 30-day mortality being almost 4 times higher compared to the general population. Mortality was significantly lower in liver than kidney, heart, and lung transplant recipients, probably because of their milder immunosuppression.³ However, no SOT cohort had lower mortality than the general population. In one study from US,⁴ COVID-19 increased hospital mortality in 2307 SOT patients only

as the result of higher comorbidity burden, but did independently increase the risk of hospital admissions compared to a propensity score-matched general population of 231 047 subjects. In another study,⁵ hospital mortality did not differ in 111 liver transplant recipients compared to the general population, but liver transplant recipients had an impressive increase in COVID-19 rates compared to the general population, the standardized incidence ratio being 191.

Another study showed that 28-day crude mortality was lower in 496 kidney transplant recipients than in 1174 hemodialysis patients (16.9% vs. 23.9%). However, kidney transplant recipients were younger and with fewer comorbidities than dialysis patients. After adjustments for these and other confounders, kidney transplant recipients had twice the mortality observed in hemodialysis patients.⁶

Finally, a recent meta-analysis including data from 265 839 individuals with COVID-19 showed that the subset of 1485 SOT recipients had pooled mortality more than 50% higher than the general population.⁷ The meta-analysis showed high heterogeneity between studies. In addition, the studies showing no difference in the mortality between SOT recipients and the general population limited the comparison to hospitalized patients with the most severe infection, a population in which outcomes are unlikely to change regardless of whether patients are transplanted or not.

Altogether, extensive studies converge to indicate that SOT recipients are, in fact, at higher risk of mortality than the general population. This, together with the low rates of response to SARS-CoV2 vaccination, defines SOT recipients—particularly those on high immunosuppressive regimens—as a very high-risk population for COVID-19 related complications.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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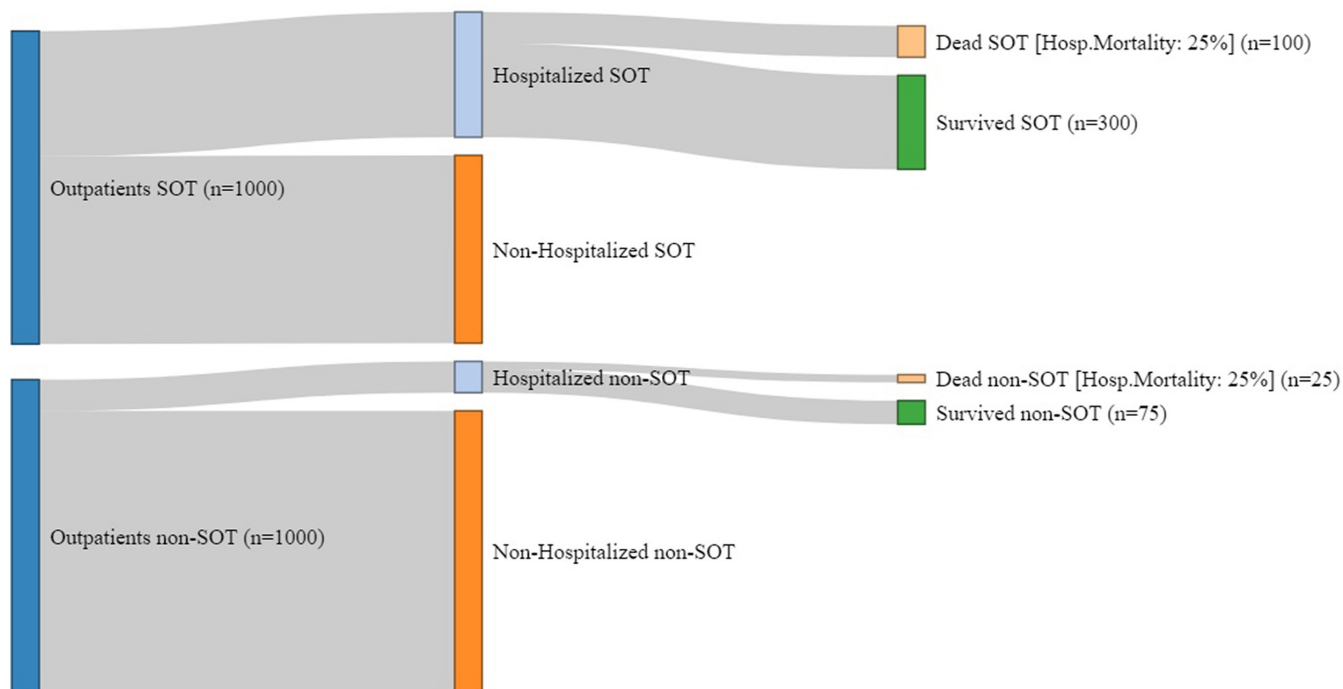


FIGURE 1 Comparison of COVID-19 associated mortality between SOT recipients and the general population. The plot shows how the analysis of hospital mortality may lead to misinterpretation of the comparison of COVID-19 related mortality between solid organ transplant (SOT) recipients and general population (non-SOT recipients). Hypothetical scenario in which the hospital mortality is 25% in both COVID-19 affected SOT recipients ($n = 1000$) and general population ($n = 1000$), but the hospitalization rate is four times higher in SOT recipients with respect to the general population, because SOT recipients are four times more likely to develop severe COVID-19 disease requiring hospitalization compared to the general population. After examining in-hospital mortality only, risk of death from COVID-19 would falsely appear equal in SOT recipients and general population (i.e., 25%) while deaths are in fact four times higher in SOT recipients ($n = 100/1000$) compared to the general population ($n = 25/1000$)

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