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Mortality in solid organ transplant recipients hospitalized for COVID-19

Solid organ transplant (SOT) recipients carry a lifelong high risk of developing severe infections, including opportunistic, community, and hospital acquired infections.[1-3] While major progress has been made in immunosuppressive drugs to prevent allograft rejection, the risk of infections remains always present because the continuing necessity of immunosuppressive drugs precludes a normal immune defense. Thus, the next question that comes to mind is: if SOT recipients are more susceptible to infections, are they also at higher risk of dying from these infections? Even though the traditional intuition suggests that lower immunity should be associated with higher mortality in the presence of a severe infection, this may not be the case. We will attempt to provide an answer to this challenging and important question in the context of the evolving evidence.

In this AJT edition, Heldman and colleagues (IN PRESS) studied the trends in mortality among SOT recipients hospitalized for COVID-19 during the course of the pandemic. The authors utilized data from a multicenter registry and compared the 28-day mortality between early and late 2020. Out of the entire registry population of 1616, approximately 60% ($N = 973$) were included in the study; data were not available in 11%, and 38% were not hospitalized. The main finding showed that the 28-day mortality decreased from 19.6% in the early period to 13.7% in the late period, which represented a significant 33% reduction in the odds of dying (adjusted odds ratio 0.67, 95% CI 0.46–0.98). The late period had a lower number of kidney recipients, less comorbidities (i.e., hypertension, diabetes, coronary artery disease, and chronic lung disease), less baseline use of corticosteroids, higher number of lung recipients, and more baseline use of anti-metabolite, all significantly different from the early period. Notably, comparing early with late period, the use of hydroxychloroquine dropped from 60% to 1%, convalescent plasma increased from 8% to 30%, remdesivir increased from 9% to 53%, and corticosteroid increased from 11% to 61%. Hence, there are several potential confounders that could have affected mortality: The significant lower number of comorbidities could explain, in part, the better survival in the late period, but the lower number of kidney and higher number of lung recipients would not favor the late period. A multivariable regression model accounting for several of these baseline comorbidity imbalances was performed by the authors, and the lower 28-day mortality persisted in the late period. On the other side, hydroxychloroquine, which has shown to be harmful by increasing mortality in hospitalized patients,[4,5] was much less used in the late period, while remdesivir and dexamethasone, both of which have shown significant clinical benefits in hospitalized patients with COVID-19,[6,7] were used more in the late period. These significant differences regarding drug treatments could also explain the study findings of better survival in the late period. The differences in convalescent plasma would not change mortality since we now have a preponderance of evidence from randomized trials that convalescent plasma is not associated with survival benefits in hospitalized patients.[8,9] Heldman's results show the challenges to find the actual reasons for improved survival. Prospective cohort or nested case-cohort studies to evaluate prognostics and rigorous randomized controlled trials to evaluate therapeutics will be needed to gain more knowledge on survival outcomes in transplant patients with COVID-19.[10] Interestingly, in line with Heldman's results, two other observational cohort studies showed no worse mortality in SOT compared to non-SOT patients with COVID-19: Rinaldi et al.[11] showed no differences even though SOT patients had higher Charlson score at baseline, and Avery et al.[12] also found no mortality differences, despite SOT recipients had more baseline comorbidities; notably SOT patients with COVID-19 showed a more rapid improvement in disease severity than non-SOT-patients.[12] Is there an evidentiary precedent to believe that SOT recipients do not have worse outcomes or may have even better outcomes than non-SOT patients with severe infections?

A study from the University of Nebraska Medical Center[13] showed for the first time that SOT patients hospitalized with sepsis and bacteremia had better survival outcomes in both a 28-day and 90-day follow-up, compared to non-SOT patients, despite the fact that SOT patients with sepsis had more comorbidities, higher SOFA score (disease severity), and more multiorgan failure—all statistically significant different at baseline; this finding of SOT better survival from sepsis was subsequently confirmed by another large population study from the University of Alabama.[14] Thus, the new scientific evidence from COVID-19 placebo-controlled double-blind trials that immunomodulators significantly improve clinical recovery and survival,[15-17] and that SOT patients do not have increased mortality (IN PRESS plus[11,12]), altogether supports the pre-COVID-19 evidence that SOT recipients are at increased risk for infections, but paradoxically are at similar or decreased risk for infection-related morality compared to non-SOT patients.[13,14]

Heldman and colleagues' findings corroborate previous studies on SOT patients' survival to severe infections and bring further light to these dark pandemic times.

KEYWORDS

clinical research/practice, infection and infectious agents, infection and infectious agents - viral, infectious disease

Andre C. Kalil
Diana F. Florescu

Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

Correspondence
Andre Kalil, University of Nebraska Medical Center, 985400 Nebraska Medicine, Omaha, NE 68198, USA.
Email: akalil@unmc.edu

ORCID

Andre C. Kalil https://orcid.org/0000-0002-6489-6294

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