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EDITORIAL

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Immunosuppression in solid organ transplant recipients with Covid-19: More data, but still complicated

Abstract

"Outcomes of COVID-19 in solid organ transplant (SOT) recipients: a matched cohort study" by Pereira et al found similar 28 day mortality among hospitalized SOT recipients and comorbidity matched controls, shedding light on the relationship between immunosuppression and Covid-19 outcomes.

When Covid-19 emerged as a global pandemic, there were concerns that immunosuppression would predispose solid organ transplant (SOT) recipients and other immunocompromised populations to more severe or fatal disease than the general population. These concerns stemmed from past experience with other respiratory viruses and from early reports of high mortality in SOT recipients.[1] Advanced age and comorbidities that are prevalent among SOT recipients have been consistently shown to be associated with mortality in Covid-19,[2] but the impact of immunosuppression on disease course in SOT recipients is less clear. The study by Pereira et al adds to a growing body of literature demonstrating that SOT recipients hospitalized for Covid-19, when carefully matched for established non-immunosuppression factors, have similar mortality to non-SOT patients.[3-9] Thus, chronic immunosuppression by itself may not independently increase the risk of death in SOT recipients who have progressed to require hospitalization for Covid-19.

Pereira et al performed a retrospective cohort study of 117 SOT recipients and 350 non-SOT controls, propensity-matched on the basis of age, sex, race, ethnicity, and the presence of obesity, hypertension, and diabetes. SOT recipients were more likely to receive Covid-19 specific therapies and more likely to be admitted to the intensive care unit (ICU), but there was no significant difference in mortality by 28 days between the SOT and non-SOT cohorts (23.08% vs 23.14%, respectively, $P = .21$). The authors postulate that chronic immunosuppression may modulate the detrimental hyperinflammatory state associated with later stages of severe Covid-19. Similar findings have been reported in other matched cohort investigations that compared SOT and non-SOT patients hospitalized with COVID-19, supporting the generalizability of these results (Table 1).

Abbreviations: ICU, intensive care unit; LTR, lung transplant recipients; RIS, reduction of immunosuppression; SOT, solid organ transplant.

Social Media (Tweet) Data by @m_pereiramd show that #COVID-19 mortality in #SOTr = matched controls, but is immunosuppression off the hook? @MadyHeldman @KatesOlivia discuss why it's complicated.

The concept that post-transplant immunosuppressive therapy could either be neutral or even advantageous in severe infection is not unique to Covid-19. In a recent prospective, matched cohort of patients with gram-negative or *Staphylococcus aureus* bacteremia, there was no significant difference in mortality between SOT and non-SOT patients.[10] SOT recipients were less likely to develop septic shock than nontransplant patients and had lower levels of IL-2 and other proinflammatory cytokines, supporting a potential advantageous role of immunosuppression in the setting of infection-mediated immune dysregulation. Use of corticosteroids to suppress excessive inflammation is also an important component of the treatment for several infections in which the host inflammatory response is thought to be detrimental, including pneumococcal meningitis, tuberculous meningitis and pericarditis, and severe pneumocystis pneumonia.

Available data suggest that the pathogenesis of Covid-19 evolves over the course of infection, with high-grade viral replication predominating during the earlier phase and intense and dysregulated inflammation later in the course of disease.[11] Thus, the effects of immunosuppression may vary by disease stage. While corticosteroids are beneficial in late severe disease, immunosuppression during the early phases of disease may ultimately cause harm by promoting viral replication, as high SARS-CoV-2 viral loads are associated with increased mortality.[12] If SOT recipients are more likely to progress to disease severe enough to require hospitalization, the overall case fatality in Covid-19 may indeed be higher among SOT recipients compared to comorbidity matched controls, even if there is no difference in mortality among the fraction of patients who require hospitalization. Pereira et al's study and other investigations that focus on hospitalized patients do not asses the potential impact of early phase immunosuppression (ie, maintenance immunosuppression in SOT recipients) on Covid-19 mortality.

An additional challenge in assessing the relationship between immunosuppression and Covid-19 mortality is the frequent reduction of immunosuppression (RIS) as a strategy to promote viral clearance during all stages Covid-19 infection. Although the number of SOT recipients who received RIS after Covid-19 diagnosis was not reported in Pereira et al's study, a large multicenter investigation of SOT recipients (80% of whom were hospitalized) found that maintenance immunosuppression was reduced in 70% of cases.[2] Thus, the overall intensity of immunosuppression during hospitalization for severe Covid-19 may not reflect the baseline (ie, pre-Covid-19) immunosuppressive state in SOT recipients. The association between RIS and Covid-19 mortality has not

TABLE 1 Matched Cohort Studies of SOT Recipients and General Populations with Covid-19

Study	SOT subjects	Mortality among SOTr	Additional outcomes among SOTr	Matched cohort	Mortality among matched cohort	Comparison to non-SOTR
Hadi et al[3a]	1740 Kidney 418 Liver 262 Heart 180 Lung	*At 30 d* 10.2% (hospitalized) 4.8 (overall) *At 60 d* 12.6% (hospitalized) 6% (overall)	31% Required hospitalization 11% Required ICU 6.7% Required mechanical ventilation 25% Developed AKI	Matched 1:1 for age, gender, race, diabetes, HTN, CAD, CHF, chronic lung disease, nicotine dependence, BMI	*At 30 d* 10.3% (hospitalized) 4.8% (overall) *At 60 d* 12.5% (hospitalized) 5.8% (overall)	**No difference in overall or hospitalized mortality at 30 d or 60 d** SOTR had a higher rate of hospitalization and acute kidney injury
Webb & Marjot et al[4]	151 Liver	22% (hospitalized) 19% (overall)	82% Required hospitalization 31% Required ICU 20% Required mechanical ventilation	Matched 1:1 for age, gender, ethnicity, diabetes, HTN, baseline creatinine, obesity	27% (overall)	**No difference in overall mortality**
Colmenero & Rodríguez-Perálvarez et al[5]	111 Liver	20.8% (hospitalized) 18% (overall)	86.5% required hospitalization 11% required ICU	Age- and gender- adjusted standardized mortality ratio from 21 717 general population patients	14.8% (overall)	**No difference in overall mortality** SOTR had a higher incidence of COVID-19 diagnosis
Molnar et al[6] ***restricted to ICU patients only**	67 Kidney 13 Liver 13 Heart 4 Lung 1 Pancreas	40% (ICU)	80% Required mechanical ventilation 37% Required RRT	Matched 1:1 for age, gender, race, ethnicity, diabetes, HTN, CAD, CHF, atrial fibrillation, chronic lung disease, CKD, chronic liver disease, active malignancy, HIV, nicotine dependence, chronic medication use, BMI	43% (ICU)	**No difference in ICU mortality at 28 d**
Miarons et al[7]	30 Kidney 13 Lung 3 Liver	37% (hospitalized)	22% Required ICU 24% Developed AKI	Matched 1:4 for age, gender, and Charlson comorbidity index	23% (hospitalized)	**No difference in hospitalized mortality at 28 d** Trend toward higher mortality in SOTR largely attributable to excess mortality among lung SOTR
Ringer et al[8]	30 SOTR	13% (hospitalized)	30% Required ICU 27% Required mechanical ventilation 7% Required RRT	Matched 1:2 for age, diabetes, HTN, BMI	13% (hospitalized)	**No difference in hospitalized mortality at 28 d**

[a]The study by Hadi et al uses the same data source as the previous study by Mansoor et al, which found no significant difference in overall mortality between liver transplant recipients with COVID-19 and a matched general population cohort.[9]

been assessed in large prospective randomized trials, but the potential impact (either harm or benefit) of RIS after Covid-19 diagnosis on mortality must be considered when interpreting findings from studies that compare hospitalized SOT recipients to control populations.

While short-term mortality among SOT recipients is similar to that of comorbidity-matched non-SOT patients hospitalized for Covid-19, there may be differential effects in specific subgroups of SOT recipients. The risk of severe and fatal viral infections due to unchecked viral replication is theoretically highest in the early post-transplant period when the effects of induction agents on lymphocyte count and function are the most profound. A series of case reports of fatal peri-transplant Covid-19 among SOT recipients raised concern that mortality from Covid-19 may be particularly high in the early post-transplant period.[1] The median time from transplant to Covid-19 in Pereira's study was 6.68 years (IQR 1.93-10.02) and the study does not specifically address mortality earlier in the posttransplant period. In a large observational study of 482 SOT recipients, induction immunosuppression within 3 months of Covid-19 was not associated with mortality, but the prevalence of recent induction was only 9%.[2] Thus, the severity of Covid-19 within the first 3-6 months following transplant may not be fully appreciated in large heterogenous studies. Lung transplant recipients (LTR) may also be a particularly vulnerable subpopulation. Reports of inpatient mortality in LTR have ranged from 30%-40%, exceeding the 15%-25% mortality rates reported in general SOT cohorts that are dominated by kidney recipients.[1,2] The findings from Pereira et al's study should be interpreted with caution for certain high-risk SOT recipients.

Even if SOT recipients do not have a substantially higher risk of dying after hospitalization for Covid-19 compared to comorbidity matched controls, there may be important differences in Covid-19 related morbidity between SOT and non-SOT patients. Pereira et al found that SOT recipients had a small but statistically significant increase in ICU admissions (32.5% vs 27.7%, $P = .01$) and were more likely to receive Covid-19 specific therapies, suggesting a possible increased risk of severe disease in SOT recipients. Several observational studies of SOT recipients with Covid-19 demonstrated hospitalization rates of 30%-80%, which is significantly higher than reports from the general population.[1,2] These estimates may be inflated by reporting biases but might also reflect a predisposition for SOT recipients to progress to more severe disease as a result of increased viral replication during the earlier stages of infection. Furthermore, there are potential delayed or indirect consequences of Covid-19 that specifically affect SOT recipients. Detection of SARS-CoV-2 in asymptomatic SOT recipients may lead to delays in post-transplant care, including biopsies or other invasive procedures. Symptomatic respiratory viral infections in lung transplant recipient may precipitate the development of chronic lung allograft dysfunction (CLAD), a leading cause of long-term morbidity and mortality after lung transplantation.[13] These SOT-specific complications are difficult to appreciate from comparative analyses that focus only on hospitalized patients and short-term mortality, but should be considered when assessing the overall impact of Covid-19 in SOT recipients relative to the general population.

How will vaccination affect Covid-19 morbidity and mortality in SOT recipients relative to the non-SOT population? SARS-CoV-2 vaccines are remarkably efficacious in preventing severe disease and death in immunocompetent adults, but efficacy in SOT recipients could be limited by immunosuppression. Humoral responses to the mRNA vaccines are diminished among SOT recipients as a result of immunosuppression, and hospitalization for severe Covid-19 among fully vaccinated SOT recipients has been reported.[14,15] Vaccines may still offer some protection against severe Covid-19 despite incomplete humoral responses, but vaccinated SOT recipients are likely to be more vulnerable to severe infection compared to vaccinated immunocompetent adults with similar comorbidities.

Pereira et al's matched-cohort study, along with other studies, have consistently reported that SOT-related immunosuppressive therapy may not have an independent detrimental effect on the later stages of Covid-19 (ie, after hospitalization). However, multiple studies have reported that SOT-related immunosuppressive therapy may significantly and negatively impact the earlier stages of SARS-CoV-2 infection and increase the likelihood of needing hospitalization, perhaps through overly permissive viral replication. Assessments of morbidity and mortality across the spectrum of infection in SOT recipients and comorbidity matched cohorts will be necessary to fully understand the relationship between immunosuppression and outcomes during future pandemics.

KEYWORDS

Covid-19, immunosuppression, solid organ transplantation

CONFLICT OF INTEREST

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