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Respiratory infection. Approach to SARS–CoV–2 infection in transplant patients

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Risk of severe COVID in solid organ transplant recipients

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ABSTRACT

Despite the fact that COVID is today not a life-threat for the general population, recipients of solid organ transplantation should be viewed as a high risk group for severe COVID. Repetitive doses of SARS-CoV-2 vaccine still fail to protect SOT recipients from infection, disease or even death caused by COVID. A more frequent need for medical care may initially place these patients at greater chances of SARS-CoV-2 infection. Immunosuppression after engrafting and underlying medical conditions that led to the practice of SOT contribute to more risk of severe infection. Immunosuppression also blunts the intensity of humoral and cellular responses after vaccination, even when several booster doses have been administered. Still, vaccination is the best strategy to prevent a fatal outcome in case of SARS-CoV-2 infection, with a particular reduction in mortality. SOT recipients should be considered a high-risk population that need yearly SARS-CoV-2 vaccination.

Keywords: COVID-19, Solid Organ Transplant recipients, risk of infection, vaccination, prognosis

The pandemic caused by the severe-acute-respiratory-syndrome coronavirus type 2 (SARS-CoV-2) has complicated the practice of solid organ transplantation (SOT) in several ways: i) reduction in the availability of donors [1]; ii) reduced response to SARS-CoV-2 vaccination; iii) risk of severe coronavirus infectious disease (COVID) from immunosuppression, both in vaccinated and unvaccinated subjects.

Focusing on the clinical evolution of COVID in patients that had undergone SOT, a large metanalysis done before the wide availability of SARS-CoV-2 vaccine demonstrated that transplanted patients had more risk of severe COVID and more mortality as compared with not transplanted individuals [2]. A total of 1,485 SOT recipients, enrolled in 15 studies with retrospective design, were evaluated; most grafts involved kidneys, but other transplanted organs as liver, heart, lungs, pancreas were included in the analysis. Other medical conditions were commonly present in transplanted subjects, as hypertension, diabetes, and chronic lung, kidney, or liver disease. The number of non-transplanted patients that served as comparators exceeded 15,000 subjects, which also had the beforementioned comorbid conditions at lower frequencies. The mean age of participants was in general comparable in all studies. The risk of need for ICU admission was greater in transplanted as compared with non-transplanted individuals (OR: 1.57 [95% CI, 1.07-2.31], p=0.02), although need of mechanical ventilation was not different between these groups (OR: 1.19 [95% CI, 0.89-1.58], p=0.24). With respect to fatal outcomes, mortality resulted significantly greater among SOT recipients as compared with controls (OR: 1.40 [95% CI, 1.10-1.79], p=0.007); this difference remained significant when transplanted patients were compared with controls matched for age, sex and comorbidities (HR: 1.42 [95%CI, 1.01-2.00], p=0.046). It may be concluded that recipients of SOT are burdened with greater morbidity and mortality associated with SARS-CoV-2 infection. The reasons for this association may be firstly the greater number of comorbidities in transplanted patients--such as hypertension, diabetes, chronic kidney, liver lung or heart disease, and others—[3, 4], so that the need of SOT may be viewed as a surrogate marker of underlying medical conditions that worsen the prognosis of COVID.

The negative effect of immunosuppressive therapy over the evolution of COVID is a subject of debate. After SARS-CoV-2 infection, the enhancement of intense immune reactions, where the release of cytokines has a central role [5], play the main part in the pathogenesis of severe COVID. Therefore, SOT recipients may see some benefits from being under treatments that blunt the overstimulation of immune responses

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against SARS-CoV-2 infection, in particular inflammatory responses [6], of which the indication of corticosteroids for patients with severe respiratory distress is a paradigmatic example [7]. Some drugs in particular, as calcineurin inhibitors or mycophenolic acid, may reduce the risk of severe COVID in part from the anti-inflammatory effect, but also with potential antiviral properties [8-10]. The negative aspect is that also T-cells producing virus-specific cytokines have been shown to be inhibited under immunosuppressive drugs [11]. In general, taking the results of different studies that analyze humoral and cellular response against SARS-CoV-2, it may be concluded that the initial immune response to primary infection may be weaker in transplanted subjects under immunosuppressive therapy, what may make infection more aggressive, although inflammatory responses may be less intense; this makes difficult to predict the net effect of immunosuppression on the severity of COVID in SOT recipients. However, survivors to COVID are capable of generating a long-lasting immunity, in part related with the greater severity of the first infection [12-15].

Given this in general more risk of complicated COVID among SOT carriers, this population was primed for early SARS-CoV-2 vaccination. As could be expected, immunosuppression is translated into lower response rates to mRNA vaccines when comparing SOT recipients –including kidney, liver, lung, heart-- to healthy individuals [16, 17]. In particular, cellular immune responses are lower in SOT recipients even when compared, not just with healthy controls, but also with other causes of immunosuppression as primary immunodeficiencies or HIV infection, defect that mostly compromises the durability of the protective effect of the vaccine [18]. In a prospective study including 200 SOT recipients (live, kidney and lungs) and another 200 controls, the humoral and cellular responses to mRNA vaccine were lower in the former after 6 months of follow-up. Positive IgG titers against the SARS-CoV-2 spike were seen in only 36% of transplanted participants, but in 97% of controls; with respect to cellular immunity response was positive in 13% versus 60%, respectively [19]. Of particular concern, it seems that lung transplant is associated with lower humoral responses after vaccination (10-40%) when compared with kidney (40-60%) or liver (30-40%) transplant [20-25].

Despite the reduced protective effect of vaccination, the benefit in transplanted patients is very significant. In a large study including nearly forty thousand SOT recipients that had received two doses of SARS-CoV-2 vaccine, vaccination was not associated with a reduction in the risk of infection, but provided a 20% reduction in the risk of death in case of COVID as compared with unvaccinated patients [26]. Again, patients with lung transplantation and subjects older than 50 years, those that have weaker response to vaccination, were found with higher risk of death. Several studies have shown that immunosuppressive regimens that include glucocorticoids, mycophenolate mofetil, calcineurin inhibitors and belatacept are associated with less response to vaccination. Still, the benefit of vaccination among transplanted individuals is greatly reduced as compared with healthy subjects. Studies done in the general population showed more than 90% vaccine efficacy

both in terms of lower rate of infections and lower mortality. It is important to emphasize that SOT recipients who received vaccine doses had a better chance of survival compared with unvaccinated SOT recipients in case of COVID.

The administration of booster doses after primary vaccination provides stronger immunity in SOT recipients, which includes humoral response, neutralizing activity, and cellular response [27]. Still, around 20% of patients with SOT may still remain seronegative after several doses of SARS-CoV-2 vaccine. However, it seems that the greater the number of vaccine doses the lower the chances for severe COVID [28]. Comparative studies suggest that mRNA vaccines have better performance that adenovirus vector vaccines in SOT carriers [29].

It may be concluded that patients with SOT are exposed to a greater risk of severe COVID, although immunosuppression is not the unique or even the major factor contributing to this worse outcome, as underlying medical conditions are also strongly associated negative factors. Although the response to vaccine is weaker in transplanted individuals, booster doses seem to improve protection but not yet to levels comparable to the general population. For all these reasons, in the current scenario of starting vaccination with the fifth or even the sixth dose of SARS-CoV-2 vaccine, SOT recipients should be considered first-line candidates for this yearly schedule that includes other high-risk populations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Pascual J, Mazuecos A, Sánchez-Antolín G, Solé A, Ventura-Aguiar P, Crespo M, et al. Best practices during COVID-19 pandemic in solid organ transplant programs in Spain. Transplant Rev (Orlando). 2023 Jan;37(1):100749.

2. Ao G, Wang Y, Qi X, Nasr B, Bao M, Gao M, et al.. The association between severe or death COVID-19 and solid organ transplantation: A systematic review and meta-analysis. Transplant Rev (Orlando). 2021; 35:100628.

3. Aziz H, Lashkari N, Yoon YC, et al. Effects of coronavirus disease 2019 on solid organ transplantation. Transplant Proc 2020; 52:2642–53.

4. Kates OS, Haydel BM, Florman SS, Rana MM, Chaudhry ZS, Ramesh MS, et al Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study. Clin Infect Dis. 2021 Dec 6;73(11):e4090-e4099.

5. Shibabaw T. Inflammatory cytokine: IL-17A signaling pathway in patients present with COVID-19 and current treatment strategy. J Inflamm Res. 2020;13:673–80.

6. Romanelli A, Mascolo S. Immunosuppression drug-related and clinical manifestation of coronavirus disease 2019: a therapeutical hypothesis. Am J Transplant 2020; 20:1947–8. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney

transplant recipients. Kidney Int 2020; 97:1076–82.

7.   RECOVERY Collaborative Group et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436

8.   Cho J, Yi H, Jang EY, et al. Mycophenolic mofetil, an alternative antiviral and immunomodulator for the highly pathogenic avian influenza H5N1 virus infection. Biochem Biophys Res Commun 2017;494:298–304.

9.   Uematsu J, Sakai-Sugino K, Kihira-Nakanishi S, et al. Inhibitions of human parainfluenza virus type 2 replication by ribavirin and mycophenolate mofetil are restored by guanosine and S-(4-nitrobenzyl)-6-thioinosine. Drug Discov Ther. 2019;13:314–21.

10. Xiao J, Song X, Deng J, et al. Inhibition of cyclophilin A suppresses H2O2-enhanced replication of HCMV through the p38 MAPK signaling pathway. FEBS Open Bio 2016;6:961–71.

11. Favà A, Donadeu L, Sabé N, Pernin V, González-Costello J, Lladó L, et al. SARS-CoV-2-specific serological and functional T cell immune responses during acute and early COVID-19 convalescence in solid organ transplant patients. Am J Transplant. 2021 Aug;21(8):2749-2761. doi: 10.1111/ajt.16570.

12. Del Bello, A.; Kamar, N.; Vergez, F.; Faguer, S.; Marion, O.; Beq, A.; Lathrache, Y.; Abravanel, F.; Izopet, J.; Treiner, E. Adaptive Lymphocyte Profile Analysis Discriminates Mild and Severe Forms of COVID-19 after Solid Organ Transplantation. Kidney Int. 2021, 100, 915–927.

13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5

14. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020 Aug 7;369(6504):718-724. doi: 10.1126/science.abc6027.

15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032..

16. Yanis A, Haddadin Z, Spieker AJ, Waqfi D, Rankin DA, Talj R, et al. Humoral and cellular immune responses to the SARS-CoV-2 BNT162b2 vaccine among a cohort of solid organ transplant recipients and healthy controls. Transpl Infect Dis. 2022 Feb;24(1):e13772. doi: 10.1111/tid.13772.

17. Miele M, Busà R, Russelli G, Sorrentino M.C., Di Bella, M.; Timoneri, F et al. Impaired Anti-SARS-CoV-2 Humoral and Cellular Immune Response Induced by Pfizer-BioNTech BNT162b2 MRNA Vaccine in Solid Organ Transplanted Patients. Am J Transplant 2021; 21:2919-2921.

18. Gao Y, Cai C, Wullimann D, Niessl J, Rivera-Ballesteros O, Chen P, et al. Immunodeficiency Syndromes Differentially Impact the Functional Profile of SARS-CoV-2-Specific T Cells Elicited by mRNA Vaccination. Immunity 2022; 55: 1732–1746.

19. Hamm SR, Møller DL, Pérez-Alós L, Hansen CB, Pries-Heje MM, Heftdal LD, et al. Decline in antibody concentration 6 months after two doses of SARS-CoV-2 BNT162b2 vaccine in solid organ transplant recipients and healthy controls. Front Immunol. 2022;13:832501.

20. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021 Jun 1;325(21):2204-2206.

21. Crespo M, Barrilado-Jackson A, Padilla E, Eguía J, Echeverria-Esnal D, Cao H, et al. Negative immune responses to two-dose mRNA COVID-19 vaccines in renal allograft recipients assessed with simple antibody and interferon gamma release assay cellular monitoring. Am J Transplant. 2022 Mar;22(3):786-800.

22. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, et al. Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant. 2021 Aug;21(8):2727-2739.

23. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021 Aug;75(2):435-438.

24. Ruether DF, Schaub GM, Duengelhoef PM, Haag F, Brehm TT, Fathi A, et al. SARS-CoV2-specific Humoral and T-cell Immune Response After Second Vaccination in Liver Cirrhosis and Transplant Patients. Clin Gastroenterol Hepatol. 2022 Jan;20(1):162-172.e9.

25. Shostak Y, Shafran N, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, et al. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. Lancet Respir Med. 2021 Jun;9(6):e52-e53.

26. Callaghan CJ, Mumford L, Curtis RMK, Williams SV, Whitaker H, Andrews N, et al. Real-world effectiveness of the Pfizer-BioNTech BNT162b2 and oxford-AstraZeneca ChAdOx1-S vaccines against SARS-CoV-2 in solid organ and islet transplant recipients. Transplantation. 2022;106(3):436–46.

27. Boyarsky B.J., Werbel W.A., Avery R.K., Tobian A.A.R., Massie A.B., Segev D.L., Garonzik-Wang J.M. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA. 2021;325:1784–1786.

28. Kumar D, Hu Q, Samson R, Ferreira VH, Hall VG, Ierullo M, et al. Neutralization against Omicron variant in transplant recipients after three doses of mRNA vaccine. Am J Transplant. 2022 Aug;22(8):2089-2093. doi: 10.1111/ajt.17020.

29. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA. 2021 May 4;325(17):1784-1786. doi: 10.1001/jama.2021.4385