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SARS-CoV-2 infection in liver transplant recipients: A complex relationship

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Abstract

The recent manuscript reviewed investigations involving liver damage in coronavirus disease 2019 (COVID-19) patients, and COVID-19 in patients with previous chronic hepatological diseases, such as patients with liver graft. The literature presents several conflicting results concerning the anti-SARS-CoV-2 response in patients with solid organ transplants, in liver transplant recipients. Therefore, we would like to humbly state a few points for consideration involving liver transplant recipients and COVID-19, such as the time since transplantation, comorbidities, and immunosuppressive regimens.

Key Words: COVID-19; SARS-CoV-2; Liver transplant; Immunosuppression; Infection; Comorbidities

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Core Tip: There is not a consensus whether solid organ transplant recipients present increased severity or death rates due to coronavirus disease 2019 (COVID-19) compared with the general population. In particular, liver allograft has a low risk of rejection, therefore enabling treatment with relatively less immunosuppressive regimens. The reduction in the production of proinflammatory cytokines, without a drastic suppression of the immune response, may benefit liver transplant recipients during COVID-19. Further investigations should compare different organ transplant

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recipients, elapsed time from the organ transplant, different immunosuppressive treatments, and their anti-SARS-CoV-2 response.

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TO THE EDITOR

We read with great interest the article entitled “Liver dysfunction and SARS-CoV-2 infection”, recently published by Gracia-Ramos *et al*[1] in the World Journal Gastroenterology[1]. Gracia-Ramos *et al*[1] performed a review on patients with liver dysfunction and coronavirus disease 2019 (COVID-19), highlighting investigations involving liver injury in COVID-19 patients, and COVID-19 in patients with previous chronic liver disease, such as cirrhosis and liver transplant recipients. Nevertheless, we would like to raise a few considerations regarding liver transplant recipients and COVID-19.

Transplantation is a treatment for organ failure and end-stage organ illnesses, requiring patients to undergo regular use of immunosuppressive treatment to avoid organ rejection[2]. There is no consensus regarding the increase in the incidence or severity of COVID-19 on solid organ transplant (SOT) recipients[3]. A few reports have identified an increase in severe COVID-19 and mortality rate in SOT recipients[4, 5], while others failed to do so[3,6].

SOT patients may respond differently to COVID-19 due to associated comorbidities, the organ grafted, elapsed time from the transplant surgery, drugs used to prevent organ rejection, or drugs used to treat SARS-CoV-2 infection[7-9]. The identification of the organ grafted is usually described in the manuscripts[6], but only one manuscript with comparison between the different organ transplant recipients has been made so far, identifying an increase in mortality in kidney and heart transplant recipients in comparison to liver transplant recipients[5].

A systematic review identified a similar death rate in liver transplant recipients and non-transplant recipients, but a higher percentage of non-transplant recipients were obese or had cardiovascular or respiratory diseases[10]. Hospitalization in the intensive care unit presented mixed results, and only one investigation reported the need for mechanical ventilation, and liver transplant recipients presented a greater need for it, in comparison to non-SOT patients[10]. Consequently, it is not possible to confirm if liver transplant recipients have a lower risk for severe illness or death risk in comparison to non-transplant recipients during COVID-19.

The liver allograft has a lower risk of rejection in comparison to heart and kidney allograft. Therefore, it is usually treated with reduced immunosuppressive regimens compared with the other SOT patients[11,12]. Different immunosuppressive regimens can affect the detection of SARS-CoV-2 RNA in nasopharyngeal swab tests[13]. Tacrolimus, a commonly used drug by SOT patients, has been shown to display anti-coronavirus effects *in vitro*[14] and putative protective properties in liver transplant recipients with COVID-19[15]. In contrast, another report identified that tacrolimus has no significant effect on the mortality risk[16].

We hypothesize that the inhibition of the calcineurin by tacrolimus could curb the production of proinflammatory cytokines, similarly to the observed in other inflammatory models[17-19], and reduce or prevent the development of the cytokine storm in COVID-19[20]. A recent report associated tacrolimus therapy with a protective effect in liver transplant recipients with COVID-19[15]. Importantly, the use of tacrolimus in association with dexamethasone in immunocompetent COVID-19 patients is currently being tested in a Spanish clinical trial (clinicaltrials.gov/ct2/show/NCT04341038).

Importantly, SOT recipients (including liver, kidney, heart, lung, and others) have an increased risk of mortality due to infections in the first year after the transplant[21], especially respiratory infections[22]. A recent review identified a higher mortality rate in patients with over a year of organ graft[23]. Another report identified no difference in elapsed time from transplant in survival and non-survival COVID-19 patients, but

patients presented a high incidence of other comorbidities[24]. In a recent report, liver transplant was not associated with greater mortality risk, while the association with other comorbidities (mainly diabetes, hypertension, obesity, and cardiovascular disease) posed a higher death risk[25]. It is reasonable to assume that comorbidities associated with poor outcomes in non-SOT patients will also influence the COVID-19 disease course in liver recipients, such as co-infection[26], respiratory disorders[27], and alcohol consumption[28]. In another report, liver transplant recipients presented similar mortality to non-SOT patients and reduced mortality in comparison with patients with liver cirrhosis[29].

On the other hand, liver transplant recipients developed lower levels of anti-SARS-CoV-2 IgG, and a more pronounced reduction in SARS-CoV-2-specific IgG levels, 6 mo after COVID-19[30]. Therefore, a long-term follow-up is necessary to fully determine the duration of the anti-SARS-CoV-2 immune response and the long-term protection offered by COVID-19 vaccines in liver transplant recipients. A recent report has identified SARS-CoV-2 infections in fully vaccinated SOT patients, and, importantly, the death of a fully vaccinated heart transplant patient due to COVID-19[30].

In conclusion, Gracia-Ramos *et al*[1] presented interesting points concerning liver transplant recipients with COVID-19. However, further investigations are needed to better understand the impact of comorbidities, elapsed time since the organ transplant, immunosuppressive regimen, and vaccination on COVID-19 in liver transplant patients.

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