

# COVID-19, liver transplant, and immunosuppression: Allies or foes?

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## Abstract

Liver transplant (LT) recipients are considered at a particularly high risk for developing critical COVID-19 infection. To date, available data are heterogeneous and scarce and mortality in LT recipients seems to be higher compared to normal population, but whether this is caused by altered immunological status, immunosuppression (IS), or underlying comorbidities has not yet been fully clarified. Some evidences show that IS might play a role in the pathophysiology of this new disease. We searched all available data regarding LT recipients infected by COVID-19, focusing on the role of IS. To date, 244 LT recipients have been reported as COVID-19-positive. Trends among transplant physicians are to reduce overall IS, especially antimetabolite drugs, but the current available observations are still not enough to build strong evidences for recommendation and IS should be meticulously tailored case by case.

## KEYWORDS

COVID-19, liver transplant, liver transplantation

## 1 | INTRODUCTION

For transplant physicians, an accurate tailoring of immunosuppression (IS) is critical to achieve the best balance between the risk of rejection and the risk of infection. The COVID-19 outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with its steady spread, has become a novel and unexplored challenge for global health care. The majority of patients experience only a mild-to-moderate and self-limiting disease. Among the clinical manifestations of severe disease, some are peculiar to COVID-19, such as severe lymphopenia and eosinopenia. In fact, severe COVID-19 disease seems to be

characterized by an excessive pro-inflammatory cytokine production, resulting in the so-called cytokine storm syndrome (CSS), which leads to the development of acute respiratory distress syndrome (ARDS), endotheliitis, thromboembolic complications, and multiorgan failure.<sup>1</sup>

Transplant recipients, compared to general population, are deemed at additional risk of developing COVID-19 severe infection due to their altered immunological status. Despite data on COVID-19 infection among liver transplant (LT) recipients are scarce and heterogeneous, minimization of immunosuppression (IS) has been recommended for LT patients with COVID-19.<sup>2</sup> This assumption is based on the clinical experience in treating other infections, where decreasing IS is a common practice. The aim of this brief communication is to summarize the most recent data on LT infected by COVID-19 and, in particular, to focus on the role that immunosuppression might have in the pathophysiology of the disease among this group of patients who have altered immunological status.

**Abbreviations:** ARDS, Acute respiratory distress syndrome; AZA, Azathioprine; CNI, Calcineurin inhibitors; COVID-19, Coronavirus disease 2019; CSS, Cytokine storm syndrome; IL-2, Interleukin-2; IS, Immunosuppression; LT, Liver transplant; MMF, Mycophenolate mofetil; MPA, Mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; NFAT, Nuclear factor of activated T lymphocytes; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ST, Corticosteroids.

## 2 | MATERIALS AND METHODS

A research within the MEDLINE and PubMed databases was carried out by two different authors (AP and FT) using the MeSH terms used were "COVID-19" (entire related MeSH terms: 2019 novel coronavirus, SARS-CoV-2 infection, 2019-nCoV infection) AND "liver transplant" from November 2019 until June 10, 2020. The electronic bibliographic database included MEDLINE-PubMed, EMBASE, Cochrane Library, and Web of Science. All original articles, letters to the editor, correspondence, case reports, clinical randomized controlled trials, non-randomized controlled trials, reviews, consensus articles, and protocol studies were included. Only papers published in English were reviewed. Data extraction, using the text, tables, and figures of the original available articles, was performed out independently by two researchers (AP and FT). The quality of the data selected was evaluated independently by two researchers (RA and TMM).

## 3 | RESULTS

As of June 10, 2020, there are 244 reported cases of LT infected by COVID-19,<sup>3-21</sup> including 240 adult and 4 pediatric LT recipients (Table 1). So far, the available data are scarce, not homogeneous, and based mainly on case reports, correspondences, and letters to the editors; thus, the analysis and the interpretation of data must be cautious. Among the largest series,<sup>9,12,19</sup> the overall mortality of LT recipients infected with SARS-CoV-2 ranged from 16% to 29%.

Of the 244 LT patients with COVID-19 reported, 41 (16.8%) died. The ELTR registry reported the largest cohort so far with 103 cases.<sup>19</sup> Out of these, 76 (74%) were male and 27 (26%) were female with a median age of 65 years (range 11-82). Comorbidities were common and included hypertension (51%), diabetes (41%), chronic renal impairment (15%), and history of smoking (13%). As expected, most patients (85%) received CNIs-based IS, but, unfortunately, information on the management of IS during the SARS-CoV-2 infection is unavailable. Notably, in this large case series the mortality rate was higher among patients with a follow-up  $\geq 2$  years from LT.<sup>19</sup> This trend is confirmed by other reports,<sup>4,18</sup> but the underlying reasons remain unclear. One potential explanation could be the longer exposure to IS therapy, a known risk factor for developing IS-related complications such as hypertension or diabetes that might play a role in increasing the mortality risk for COVID-19. On the other hand, other publications are discordant reporting a greater mortality rate among patients transplanted within the last 2 years.<sup>9</sup>

## 4 | DISCUSSION

Calcineurin inhibitors (CNIs) are the mostly used IS drugs after LT and are considered the mainstay in IS maintenance regimens.

CNIs, namely cyclosporine and FK506 (tacrolimus), acquire activity after binding the cyclophilin or FKBP-12. Their interaction with calcineurin blocks the transfer of the nuclear factor of activated T lymphocytes (NFAT) in the nucleus. NFAT is necessary for the induction of the cytokine gene expression, like the interleukin-2 (IL-2). The blockage of NFAT dephosphorylation leads to the no response of T lymphocytes to specific antigenic stimuli. Thus, the IL-2-dependent growth and differentiation is blocked.<sup>22</sup> Looking specifically into the SARS-CoV family, experimental studies demonstrated molecular interactions between calcineurin/NFAT pathway, CNIs, and CoV non-structural protein 1 (Nsp1). In particular, both cyclosporine and FK506 blocked the replication of human and animal SARS-CoV *in vitro*.<sup>23-27</sup> Even though these are experimental models, *in vitro* evidences showed that both cyclosporin and tacrolimus might have a potential role in inhibiting SARS-CoV replication.

Antimetabolites drugs, such as mycophenolate mofetil (MMF), mycophenolic acid (MPA), and azathioprine (AZA), are also commonly used after LT. They work by disrupting the making of RNA and DNA, thus hindering the replication of T and B lymphocytes. In COVID-19 patients, the significant decrease in total number of B cells, T cells, and NK cells leads to the dysregulation of immune response. Notably, these patients show a pronounced lymphopenia and low counts of CD3+ and CD4+ cells and memory helper T, while the percentage of naïve helper T cells seems to be increased.<sup>28</sup> In this scenario, antimetabolite drugs have an inherent potential to cause lymphopenia and/or impair lymphocyte function, thus overlapping with COVID-19 effects of inducing lymphopenia, with a potential additional risk for LT recipients.

The mammalian target of rapamycin inhibitors (mTORis), namely sirolimus and everolimus, acts through the interaction with an immunophilin, FKBP-12, subsequently forming a complex. The latter inhibits the target kinase of rapamycin (mTOR), which is a key enzyme in the progression of the cell cycle, thus blocking the growth of T lymphocytes. So far, no study demonstrated the feasibility and safety of the mTORis as antiviral therapy for COVID-19. As of June 2020, there is an ongoing clinical randomized controlled trial (NCT04341675) with the aim to determine whether treatment with sirolimus can improve clinical outcomes in hospitalized patients with COVID-19.

Finally, corticosteroids (ST) are well-known IS drugs and might be given as maintenance therapy after solid organ transplantation. ST were widely used in patients with COVID-19 due to their ability to modulate a variety of involved cytokines. However, their utilization for COVID-19 is still controversial and there is no final consensus. A report from China stated that ST treatment is a double-edged sword and recommends short courses of corticosteroids at low-to-moderate dose, used prudently, for critically ill patients with 2019-nCoV pneumonia.<sup>29</sup>

The management of IS in LT patients with COVID-19 has been heterogeneous among different reports, and substantial data on the incidence of rejection are lacking. The majority tend to reduce the IS dosages, mainly tapering or discontinuing the antimetabolite drugs. In addition, the severity of the disease and the need for intensive care

**TABLE 1** COVID-19 infection in liver transplant (LT) patients

Authors	Patients (n), age, gender	Major comorbidities	Clinical characteristics	Diagnostic tests	Baseline IS	Pharmacological treatment	IS modifications	Outcomes
D'Antiga L <sup>3</sup>	3 Children	NA	None	RT-PCR	NA	None	No	Alive
Gao F et al <sup>11</sup>	37 y M 50 y M 59 y M	1 Previous HBV 1 NA 1 Previous HBV	Fever (100%), cough, jaundice	RT-PCR, CT chest	• Tac + Iv MPA • Low Tac (0.03 mg/kg/d) • Tac + MMF	• Oseltamivir, Abx, Rh-GCSF, IV-Ig • α-IFN, umifenovir, and lop/rif, IV-Ig • α-IFN, arbidol, and lop/rif, IV-Ig	• Lowering Tac and MPA • Discontinued Tac • No	Alive Alive Died (33%)
Bhoori S et al <sup>4</sup>	6, data available for 3 M (50%)	HTN (50%) DM (50%) BMI > 25 (50%)	NA	RT-PCR	Low dose CS 2 Low dose Tac 1	NA	No	Died 3 (50%)
Fernández-Ruiz M et al <sup>5</sup>	6 3 M (50%) 3 F (50%)	HTN 3 (50%) DM 4 (66%) CKD 1 (16%) HBV 2 (33%) HCV 3 (50%)	Fever 4 (66%) SOB 4 (66%) Cough 3 (50%) Malaise 3 (50%) Diarrhea 3 (50%) Myalgia 1 (16%)	RT-PCR	Tac 2 (33%) Eve 1 (16%) MMF 1 (16%) MMF + Eve 1 (16%) ST + AZA + Eve 1 (16%)	HCQ 4 (66%) IFN-β 2 (33%) Lop/Rit 2 (33%) None 2 (33%)	No 3 (50%) Discontinuation MMF 1 (16%) Transitory conversion to Tac 2 (33%)	No rejections Died 2 (33%)
Lagana SM et al <sup>6</sup>	1 6 mo old LDLT	Biliary atresia	Fever SOB Diarrhea	RT-PCR	NA	HCQ	Augmented for rejection. ST and MMF tapered	Alive
Pereira MR et al <sup>7</sup>	13 LT among 90	NA	NA	RT-PCR	NA	NA	NA	Overall 32 died
Kates OS et al <sup>8</sup>	1 M 67 y	Graft cirrhosis	Cough Fatigue Diarrhea	RT-PCR	CS (target 100-150 ng/mL)	None	No	Alive
Webb GJ et al <sup>9</sup>	39 25 M (64%) 14 F (36%)	HTN 18 (46%) DM 15 (38%) BMI > 25.26 (66%) CAD 6 (15%)	NA	RT-PCR	Tac 35 (89%) MMF 20 (51%) ST 16 (41%) Sir 2 (5%)	NA	NA	Died 9 (23%)
Hammami MB et al <sup>10</sup>	1 M 63 y	HCV ESRD DM HTN CVD Smoking	Fever Cough Fatigue	RT-PCR	Tac 1.5 BD (target 2-4 ng/mL)	Abx AZT HCQ Tocilizumab	No (target 4-6 ng/mL)	Alive
Lee BT et al <sup>12</sup>	38 overall 32 LT (84%) 6 LT + KT (16%) 26 male (68%)	HTN (63%) DM (47%) CVD (29%) CKD (63%)	Fever (61%) Cough (55%) SOB (34%) Myalgia (24%) GI (42%)	RT-PCR	Tac (97%) MMF (50%) ST (39%) CS (3%) Eve (3%)	Available for 24 pts: • 18 (75%) HCQ ± AZT • ACT 8 (33%) • Iv ST 5 (21%)	Available for 24 pts: decreased IS 19 (79%)	7 (29%) Died

(Continues)

TABLE 1 (Continued)

Authors	Patients (n), age, gender	Major comorbidities	Clinical characteristics	Diagnostic tests	Baseline IS	Pharmacological treatment	IS modifications	Outcomes
Hoek RAS et al <sup>13</sup>	1	NA	NA	RT-PCR	Tac	NA	No	alive
Verma A et al <sup>14</sup>	5 M (100%)	BMI > 25 HTN 1 (20%) DM 1 (20%) UC 1 (20%)	Fever 2 (40%) Cough 2 (40%) Other 2 (40%)	RT-PCR	CNI 1 (20%) CNI + ST 2 (40%) CNI + ST+Aza 1 (20%) MMF + ST 1 (20%)	Remdesivir 1 (20%) Abx 1 (20%)	No 4 (80%) MMF stopped and ST doubled 1 (20%)	Alive
Fung M et al <sup>15</sup>	1 F 80yo	HTN CAD DM CKD BMI > 25	SOB	RT-PCR	Tac 0.5 BD, MMF 500 mg BD	Abx	No	Alive
Müller H et al <sup>16</sup>	1 M 55 y	HIV	Fever, fatigue	RT-PCR	Tac + MMF	Abx	No	Alive
Yi SG et al <sup>17</sup>	3 LT 1 LT + KT	NA	NA	RT-PCR	NA	NA	NA	All alive
Patrono D et al <sup>18</sup>	10 total 8 M 2 F	NA	Fever 7 (70%) Cough 3 (3%) SOB 1 (10%) Diarrhea 2 (20%) Myalgia 1 Sore throat 1	RT-PCR	Tac + MMF 4 (40%) Tac + Eve 2 (20%) Tac + MMF + ST 2 (20%) Tac + ST 1 (10%) Tac 1 (10%)	HCQ 6 (60%) ST 2 (20%) HCQ + Lop/Rit 1 (10%) HCQ + ST + DRV/RTV 1 (10%) No 3 (30%)	Stop Tac 4 (40%) Stop or decreased MMF 3 (30%) Increased ST 1 (10%) No 3 (30%)	Alive 8 Died 2 (20%)
Belli LS et al <sup>19</sup>	103 total 76 M (74%) 27 F (26%) Age 65 (11–82)	BMI > 25 (56%) HTN (51%) DM (41%) CKD (15%) Smoking (13%) CAD (7%) Others (12%)	Fever (70%) Cough (59%) SOB (34%) Diarrhea (24%) Asthenia (20%) Myalgia (15%) Anosmia or dysgeusia (9%) Others (15%)	RT-PCR in 100 (97%)	86 (85%) Tac NA (15%)	HCQ (66%) AZT (33%) Lop/Rit (17%) Steroids (18%) Tocilizumab (7%)	NA	16 (16%) Died
Hann A et al <sup>20</sup>	3	HTN 2 (66%) DM 3 (100%) CKD 2 (66%) BMI > 25 3 (100%) UC 1 (33%)	Fever 3 (100%) SOB 3 (100%) Cough 1 (33%) Myalgia 1 (33%) Diarrhea 1 (33%)	NA	Tac 3 (100%) Aza 3 (100%) ST 3 (100%)	NA	NA	Alive 2 Died 1 (the one with higher IS)
Massoumi H et al <sup>21</sup>	5	NA	NA	RT-PCR	Tac 5 MMF 5	NA	NA	All alive

Abbreviations: Abx, antibiotics; ACT, anticoagulation therapy; AZA, azathioprine; AZT, azithromycin; BD, twice daily; CAD, cardiac artery disease; CKD, chronic kidney disease; CNIs, calcineurin inhibitors; CS, cyclosporine; CVD, cardiovascular disease; DM, diabetes; DRV/RTV, darunavir/ritonavir; ESRD, end-stage renal disease; EVE, everolimus; HCQ, hydroxychloroquine; HTN, hypertension; IFN, interferon; IS, immunosuppression; KT, kidney transplant; LDLT, living-donor liver transplant; Lop/Rit, lopinavir/ritonavir; LT, liver transplant; MMF, mycophenolate; OD, once daily; POD, post-operative day; Sir, sirolimus; ST, steroids; Tac, tacrolimus; UC, ulcerative colitis.

support might have also interfered with the overseeing of IS. Last but not least, it is difficult to assess whether the pharmacological treatments for COVID-19, such as hydroxychloroquine or antivirals, also played a role, as their use was not uniform across the different reports.

Although in vitro results, as discussed above, show a possible effect of IS regimen on COVID-19, its underlying mechanisms remain unclear. Initially, IS might attenuate the inflammatory response, contributing to mitigate the CSS. However, IS might also amplify the viral damage resulting in increased rates of clinically severe COVID-19 infections. A modification of the IS regimen may be considered according to the clinical conditions of the patients. On this regard, tapering IS in LT recipients has been demonstrated to be feasible without increasing the risk of rejection,<sup>30,31</sup> potentially allowing more IS manageability in these patients. Currently, based on available data, mortality among LT recipients seems to be increased compared to the non-transplant population, but whether this is caused by immunological status, IS, or underlying comorbidities has not yet been fully clarified.

In conclusion, the level of evidence provided by the currently available observations is insufficient to develop conclusive clinical recommendations and the real effects of SARS-CoV in LT recipients remain indefinite. At this stage of the pandemic, we should meticulously tailor IS for every LT recipient affected by COVID-19, carefully evaluating case by case and balancing the risk of rejection, which could potentially be more harmful than IS itself.

With this report, we would like to make a request to all the physicians dealing with LT to document in detail all COVID-19 cases, with particular attention to the IS management. Only gathering uniform and comparable data, we will better understand whether these indispensable drugs could be our friends or our foes during these uncharted times.

## CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest regarding the publication of this manuscript.

## AUTHOR CONTRIBUTION

MFDM and AP conceived the study. AP and RA designed the study. AP and FT acquired the data. RA and TMM analyzed and interpreted the data. AP and TMM wrote the manuscript. MFDM, GT, and PM edited the manuscript. MFDM, FT, GT, RA, and PM reviewed the manuscript.

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