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REVIEW

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# SARS-CoV2 and immunosuppression: A double-edged sword

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## Abstract

Severe acute respiratory syndrome Coronavirus 2 (SARS-Cov2) outbreak has caused a pandemic rapidly impacting on the way of life of the entire world. This impact in the specific setting of transplantation and immunosuppression has been poorly explored to date. Discordant data exist on the impact of previous coronavirus outbreaks on immunosuppressed patients. Overall, only a very limited number of cases have been reported in literature, suggesting that transplanted patients not necessarily present an increased risk of severe SARS-Cov2-related disease compared to the general population. We conducted a literature review related to the impact of immunosuppression on coronavirus infections including case reports and series describing immunosuppression management in transplant recipients. The role of steroids, calcineurin inhibitors, and mycophenolic acid has been explored more in detail. A point-in-time snapshot of the yet released literature and some considerations in relation to the use of immunosuppression in SARS-Cov2 infected transplant recipients are provided here for the physicians dealing with immunocompromised patients.

**KEYWORDS**

Coronavirus, COVID-19, cyclosporine, SARS, steroids, tacrolimus

## 1 | INTRODUCTION

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2) is a new virus causing a zoonosis originating from bats (COronaVIrus Disease-19, COVID-19), as recently reported in the literature. Following its outbreak in China, SARS-CoV2 has led to a worldwide spread, being declared by the WHO as a pandemic condition on March 11, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). As of June 21, 2020, 8 938 672 infected patients have been identified worldwide, 467 114 (5.2%) of whom died (https://www.worldometers.info/coronavirus/).

The leading cause of mortality is the acute respiratory distress syndrome (ARDS) following viral pneumonia. ARDS can translate into a devastating end-stage lung disease for which treatment options are limited. Furthermore, many ARDS cases may progress to pulmonary fibrosis, another clinically devastating lung disease for which also limited curative strategies are available. Therefore, understanding the immunological mechanisms of virus-related ARDS represents a high-priority research topic.

When epidemics occur, transplant patients raise concern due to their vulnerability to infections. Whether immunosuppressants modify the transition from SARS-CoV2 contagion to pneumonia and, ultimately, ARDS is not known yet.

The role of the immunological mechanisms causing coronavirus (CoV)-related ARDS in the context of transplantation can be seen as

**Abbreviations:** ARDS, acute respiratory distress syndrome; CNI, calcineurin inhibitors; CoV, Coronavirus; COVID-19, Coronavirus disease-19; CyA, cyclosporine; MERS, Middle East respiratory syndrome; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TAC, tacrolimus.

a "bench to bedside" type experiment on the impact of immunosuppressive drugs in the course of the respiratory disease.

The pathogenesis of CoV-related ARDS includes complement and coagulation cascade activation, and proinflammatory and profibrotic cytokine responses. After infecting the pneumocytes, CoV induces a massive signaling response in infected lungs, favoring thereby the release of several proinflammatory cytokines and chemokines, including IL-6, TNFα, IL-1β, and CCL2. These molecules recruit inflammatory cells to the site of infection, such as neutrophils and cytotoxic T cells. These cells may damage tissues leading to vascular leakage and fibrosis formation.[1]

In some cases, the inflammatory status can become systemic, leading to a cytokine storm syndrome with the characteristics of a secondary hemophagocytic lymphohistiocytosis. Therefore, the use of immunosuppressants such as corticosteroids or anti-cytokine drugs like IL-1 blockade (anakinra) and IL-6 receptor blockade (tocilizumab) has been proposed.[2]

With the present work, we aimed to review the existing literature on the impact of immunosuppression on coronaviruses infections and the development of severe lower respiratory tract disease. Secondly, we retrieved and summarized the recently published literature describing the course of CoV infections in transplant recipients.

## 2 | METHODS

A review of the literature reporting on coronavirus infections in immunocompromised patients was conducted. In particular, we focused on the relationship with the most frequently employed immunosuppressants in the management of transplant recipients (namely: steroids, calcineurin inhibitors, and mycophenolic acid). Secondly, an electronic search was performed to identify all studies reporting on the management of immunosuppression in transplant recipients infected with SARS-CoV2. The PubMed/MEDLINE database was searched on May 6th, 2020. The search strategy was "SARS-CoV2" OR " COVID-19" AND "transplantation". We included all the studies describing the management of immunosuppression in transplant recipients. Potential case duplicates were ruled out by analysis of demographic characteristics of the included patients and country and institution of origin of the reports.

## 3 | IMMUNOCOMPROMISED PATIENTS AND CORONAVIRUSES

Several studies reported the specific role of an immunocompromised status as a possible risk factor for CoV-related pneumonia. A study based on 85 immunocompromised vs 1152 non-immunocompromised children did not show a different prevalence of CoV-related pneumonia and severe pneumonia (22% vs 26% and 15% vs 11%, respectively). However, the immunocompromised status was a risk factor for severe respiratory disease.[3]

Another study on five Rhesus macaques showed that immunosuppression with cyclophosphamide and dexamethasone leads to a significantly higher level of the Middle East respiratory syndrome (MERS)-CoV replication in the respiratory tissues. Despite this increased viral replication, pathologic findings in the lungs were significantly lower than in immunosuppressed animals.[4]

A Korean study reported atypical presentations of MERS-CoV infection in three immunocompromised patients with delayed development of symptoms, a prolonged incubation period, and a persistent viral shedding without clinical deterioration.[5] All these peculiar presentations were probably influenced by the underlying immunological status of the patients, including the use of immunosuppressants.[5]

More recently, a systematic review analyzed 110 immunosuppressed patients infected with SARS-CoV-2, mostly presenting cancer, along with transplantation and immunodeficiency. The results revealed a tendency toward a favorable disease course, as compared to the general population. The authors concluded that this phenomenon might be explained by a possible protective role of a weaker immune response, determining a milder disease presentation and, thus, underdiagnosis.[6]

## 4 | STEROIDS AND CoV-RELATED PULMONARY DISEASE: PROS AND CONS

Understanding the potential harm or benefit of steroids in CoV-related disease is of immediate clinical importance. In theory, steroids may play a role in suppressing virus-driven lung inflammation, although increasing the time of viral clearance and viral shedding.

In Table 1, the effect of steroids on coronavirus clearance and patient survival is displayed.

**TABLE 1** Effect of steroids administration in the presence of viral pneumonia caused by coronaviruses

| Virus | Impact on viral clearance | Impact on survival |
|---|---|---|
| MERS-CoV | Delayed clearance of viral RNA from respiratory tract[7] | 90-d mortality OR = 0.8 (95% CI = 0.5-1.1; $P = .12$)[7] |
| SARS-CoV | Delayed clearance of viral RNA from the blood[8,9] | In case of severe pneumonia, protective effect (0/60 deaths vs 11/130; $P = .018$[10] |
| SARS-CoV2 | Delayed clearance of viral RNA from respiratory tract[11] | HR = 0.38 (95% CI = 0.2-0.7)[12] |

*Note:* The steroids adopted were: hydrocortisone, methylprednisolone, dexamethasone, and prednisolone.

Abbreviations: CoV, coronavirus; HR, hazard ratio; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

In a retrospective study, including 309 adults with MERS-CoV-caused ARDS, the administration of steroids did not lead to different 90-day mortality (odds ratio = 0.8, 95% CI = 0.5-1.1; $P = .12$). Conversely, delayed clearance of viral RNA from the respiratory tract secretions was reported (hazard ratio = 0.4, 95% CI = 0.2-0.7; $P = .0005$).[7]

A meta-analysis based on the steroidal treatment of SARS-CoV identified four studies only with conclusive data, all of them showing a harmful effect.[8] The adverse reported effects were (a) worsening of SARS-related psychosis, (b) increase of viremia in non-critically ill patients, and (c) development of diabetes and avascular necrosis.[9]

A Chinese study, including 190 patients with severe SARS-related pneumonia, randomly allocated the patients to four different treatment regimens. The best results were obtained in the cohort of 60 patients receiving early high-dose steroids and nasal continuous airway-positive pressure ventilation (zero deaths vs 8.5% cumulatively reported in the other three groups; $P = .018$).[10]

Up to now, the studies related to SARS-CoV2 treatment are preliminary. One study from China, including 292-positive SARS-CoV2 patients, compared steroid against non-steroid-treated groups. In the steroid group, a longer duration of viral RNA detection was revealed in the oro-pharyngeal (15 vs 8 days, $P = .013$) and feces swabs (20 vs 11 days, $P < .001$).[11]

Another Chinese study on SARS-CoV2-related ARDS showed that treatment with methylprednisolone decreased the risk of death from 61.8% to 46.0% (HR = 0.38; 95 %CI = 0.20-0.72).[12]

A third study from China on 46 severe patients with COVID-19 pneumonia showed better results in the subgroup of 26 cases receiving low-dose methylprednisolone (1-2 mg/kg/d iv for 5-7 days). The steroid group had a faster improvement of SpO2, shorter interval of oxygen supplementation (8 vs 14 days; $P < .001$), and an inferior need for mechanical ventilation ($P = .05$).[13]

Two recently published letters related to the use of steroids express controversial opinions; one considers the use of steroids as a contraindication, the other as a (cautiously) useful tool for severely diseased SARS-CoV2 patients.[14,15] Current interim guidance from WHO on clinical management of severe acute respiratory infection (released March 13, 2020) advises not to use steroids unless indicated for another reason.[16]

In transplanted patients, steroids are used mainly as induction and anti-rejection agents and always less often as a "maintenance therapy". The recently published clinical recommendations from the American Association for the Study of Liver Diseases (AASLD) have reported that minimization of high-dose steroid dosage is recommended in immunosuppressed patients with COVID-19 but maintaining a sufficient dosage to avoid adrenal insufficiency.[17] Another statement recommended initiating therapy with steroids in patients with liver disease with or without COVID-19 who have strong indications for treatment like autoimmune hepatitis or graft rejection.[17]

## 5 | OTHER IMMUNOSUPPRESSANTS AND CORONAVIRUSES: FROM BENCH TO BEDSIDE?

Various studies explored the impact of calcineurin inhibitors (CNI) cyclosporine (CyA) and tacrolimus (TAC) and their non-immunosuppressive derivatives on the in vitro and in vivo replication of coronaviruses.[18-22]

CyA and TAC bind to different cellular cyclophilins in order to inhibit calcineurin, a calcium-calmodulin-activated serine/threonine-specific phosphatase. The calcineurin inhibition blocks the translocation of the nuclear factor of activated T cells from the cytosol into the nucleus, thereby preventing the transcription of several genes encoding for the key cytokines involved in the immunological mechanisms, like interleukin-2. Apart from this mechanism, cyclophilins are required by several viruses for their replication.[18] Interestingly, inhibition of cyclophilin by CyA can block the replication of CoV of all *genera*, including SARS-CoV, human CoV-229E, human CoV-NL-63, feline CoV, as well as avian infectious bronchitis virus.[19] Similarly, TAC strongly inhibits the growth of human coronaviruses SARS-CoV, human CoV-NL63, and human CoV-229E.[20] In vitro and human ex vivo explant cultures reported the synergic effect of two immunomodulatory agents, namely interferon-alpha and cyclosporine, as critical agents for the reduction of MERS-CoV replication.[21]

Mycophenolic acid has also been shown to block the papain-like protease of MERS-CoV, therefore, blocking the in vitro replication of the virus.[23]

Due to the small number of reported transplant cases experiencing CoV infections, no clear clinical evidence exists on the real impact of the immunosuppressive drugs in the clinical practice yet. The AASLD interestingly stated that: "the immune response may be the main driver for pulmonary injury due to COVID-19 and that immunosuppression may be protective".[17] However, the recommendations for good clinical practice from most scientific societies are based on common sense rather than on evidence, as the latter is still lacking.[17,24]

## 6 | CoV-RELATED DISEASE AND SURVIVAL IN TRANSPLANTED PATIENTS

Only anecdotal experiences of solid organ transplant recipients experiencing CoV infections have been reported during SARS and MERS epidemics.[25,26] Remarkably, among the 774 and 912 deaths reported in the two outbreaks of SARS in 2002 and MERS in 2012, respectively, only two transplanted cases were described in the literature.[25,26] Likely, this number is an underestimation of reality, but it could reflect that transplant patients did not suffer from more severe forms of pulmonary disease compared to the general population during the previous CoV epidemics.

Conversely, a more significant number of case reports and small series are consistently being published during the SARS-CoV-2

**TABLE 2** Solid organ transplant patients experiencing SARS-CoV-2-related disease: details of immunosuppression modification

| Author/Country/N | Ref | Age (y) | Sex | Transplant | Time from transplant | Baseline IS | IS after CoV infection |
|---|---|---|---|---|---|---|---|
| Alberici Italy N = 20 | 27 | 59* | M 80% | Kidney 20 | 13 y* | TAC 95% MMF 70% Ster 65% mTORi 10% | IS stop/Ster iv |
| Akalin USA N = 36 | 28 | 60* | M 72% | Kidney 36 | NR | TAC 97% Ster 94% MMF 86% | MMF stop 86%/TAC stop 21% |
| Banerjee UK N = 7 | 29 | 48 | M | Kidney | 31 y | AZA Ster | None |
| | | 67 | F | Kidney | 1 y | TAC MMF Ster | TAC ↓ MMF stop |
| | | 54 | F | Kidney | 3 mo | TAC MMF Ster | TAC MMF stop |
| | | 65 | M | Kidney | 1 y | TAC MMF Ster | MMF stop |
| | | 69 | F | Kidney | 1 mo | TAC MMF Ster | MMF stop |
| | | 54 | M | Kidney | 7 y | TAC MMF | MMF stop |
| | | 45 | M | Kidney | 3 y | TAC AZA Ster | AZA stop/TAC ↓ Ster ↑ |
| Bhoori Italy N = 6 | 30 | >65 | M | Livers 3 | >10 y | CsA = 2 TAC = 1 | NR |
| | | NR | NR | Livers 3 | <2 y | CsA or TAC | NR |
| Billah USA N = 1 | 31 | 44 | M | Kidney | 7 y | TAC MMF Ster | TAC ↓ Ster iv |
| Boyarsky USA N = 148 | 32 | NR | NR | Kidney 103; Liver 23; Heart 13; Lung 9 | NR | NR | NR |
| Bussalino Italy N = 1 | 33 | 32 | M | Kidney | 2 y | TAC MMF Ster | TAC ↓ MMF ↓ Ster |
| Chen China N = 1 | 34 | 49 | M | Kidney | 6 y | TAC MMF Ster | TAC MMF stop |
| Columbia NY USA N = 15 | 35 | 51 | M 65% | Kidney | 49 mo* | TAC 93% MMF 80% Ster 67% Belatacept 13% | MMF stop 71%/All IS stop 14% TAC/MMF Ster 7% |
| Fernández-Ruiz Spain N = 18 | 36 | 71* | M 72% | Kidney 8; Liver 6; Heart 4 | 9.3 y* | TAC 50% MMF 56% Ster 61% mTOR 28% CsA 17% | TAC stop/ mTOR initiated = 2 |
| Gandolfini Italy N = 2 | 37 | 75 | M | Kidney | 10 y | TAC MMF Ster | TAC MMF stop |
| | | 52 | F | Kidney | 8 mo | TAC MMF Ster | TAC MMF stop |
| Guillen Spain N = 1 | 38 | 50 | M | Kidney | 4 y | TAC EVE Ster | TAC EVE stop |
| Hsu USA N = 1 | 39 | 52 | F | Kidney | 8 mo | TAC MMF Ster | TAC MMF stop |
| Huang China N = 2 | 40 | 51 | M | Bone marrow | 8 mo | CsA | CsA stop Ster iv |
| | | 58 | M | Kidney | 12 y | MMF Ster | Ster iv |
| Huang China N = 1 | 41 | 59 | M | Liver | 2 y | TAC MMF | TAC ↓ MMF ↓ Ster |
| Johnson USA N = 1 | 42 | 57 | M | Kidney | 8 mo | TAC MMF | MMF↓ TAC ↓ |
| Kates USA N = 4 | 43 | 54 | M | Kidney | 20 y | TAC MMF | Ster initiated/ TAC ↓ MMF stop |
| | | 67 | M | Liver | 19 y | CsA | Unchanged |
| | | 53 | F | Lung | 20 y | CsA AZA Ster | Unchanged |
| | | 74 | M | Heart | 23 y | TAC | Unchanged |
| Li China N = 2 | 44 | 51 | M | Heart | 17 y | TAC MMF | TAC MMF stop/Ster iv |
| | | 43 | M | Heart | 2 y | TAC MMF | NR |
| Liu China N = 1 | 45 | 50 | M | Liver | 2 y | TAC | TAC stop/Ster iv |
| Maggi Italy N = 2 | 46 | 61 | M | Liver | 9 d | Basiliximab TAC Ster | NR |
| | | 69 | M | Liver | 22 d | Basiliximab TAC Ster | NR |
| Marx France N = 1 | 47 | 58 | M | Kidney | 3 y | BLT MMF Ster | BLT MMF stop/CsA initiated |
| Mathies Germany N = 1 | 48 | 77 | M | Heart | 17 y | SIR MMF | TAC initiated/SIR MMF stop |
| Meziyerh Netherlands N = 1 | 49 | 35 | M | Kidney | 4 y | EVE Ster | EVE ↓ and later stop CsA stop |
| Ning China N = 1 | 50 | 29 | M | Kidney | 1 y | MMF CsA Ster | None |
| Qin China N = 1 | 51 | 37 | M | Liver | 19 d | TAC Ster | TAC Ster ↓ |

(Continues)

**TABLE 2** (Continued)

| Author/Country/N | Ref | Age (y) | Sex | Transplant | Time from transplant | Baseline IS | IS after CoV infection |
|---|---|---|---|---|---|---|---|
| Seminari Italy N = 1 | [52] | 50 | M | Kidney | 4 y | TAC MMF | None |
| Zhang China N = 5 | [53] | 38 | M | Kidney | NR | TAC MMF Ster | MMF stop |
| | | 64 | M | Kidney | | SIR MMF Ster | SIR MMF stop/Ster stop 16 d/ TAC initiated |
| | | 37 | F | Kidney | | TAC MMF Ster | MMF stop |
| | | 47 | M | Kidney | | TAC MMF Ster | MMF stop/Ster stop 4 d |
| | | 38 | M | Kidney | | TAC MMF Ster | NR |
| Zhong China N = 2 | [54] | 37 | M | Liver | 9 d | TAC Ster | TAC stop |
| | | 48 | M | Kidney | 17 y | TAC MMF | TAC ↓ MMF stop/Ster iv |
| Zhu China N = 1 | [55] | 52 | M | Kidney | 12 y | TAC MMF Ster | TAC MMF stop |

Abbreviations: AZA, azathioprine; BLT, belatacept; CHKT, combined heart-kidney transplant; CsA, cyclosporin-A; EVE, everolimus; F, female; IS, immunosuppression; M, male; MMF, mycophenolate mofetil; N, number of cases; NR, not reported; Ref, reference; SIR, sirolimus; Ster, steroids; TAC, tacrolimus; y, years.

*Median.

pandemics, many of which also reporting the details on the immunosuppressive regimen management (Table 2).[27-55]

A total of 284 COVID-19 transplant cases have been reported to date: specifically, 210 kidneys, 42 livers, 21 hearts, 10 lungs, and one bone marrow cases. The median age reported was 52 years. The cases came from the US (n = 206), Italy (n = 32), Spain (n = 19), China (n = 17), United Kingdom (n = 7), France (n = 1), Germany (n = 1), and the Nederland (n = 1). One study contains results from a nation-based survey from the USA on kidney transplantation.[32] Therefore, overlap with cases from the other articles coming from US institutions could not be ruled out.[28,31,35,39,42,43]

Out of the 130 patients in whom information on the final clinical course were provided, 30 (23.1%) deaths were reported. Globally, 67 of 280 (23.9%) cases required invasive ventilation (Table 3).[27-55]

According to these data, the current COVID-19 pandemics has sadly affected the transplant population much more in-depth respect to the SARS and MERS outbreaks.

Data reported by The Transplant Society (TTS) interestingly observed that high mortality rates (15%-30%) were mainly reported in transplant recipients from countries with high COVID-19 incidence and high mortality rates in the general populations. On the opposite, low-incidence and mortality rates were reported in transplant patients from low-incidence countries (https://tts.org/11-tts/news/692-tts-coronavirus).

When data from large registries were reported, high fatality but low prevalence rates were observed. As an example, the European Renal Association Registry reported 231 (19.1%) deaths in 1,211 kidney transplant cases (https://era-edta-reg.org/index.jsp?p=covid19).

Another large database, namely the European Liver Transplant Registry, explored the number of COVID-19-positive liver transplant candidates and recipients, reporting a similarly small prevalence (only 33 and 190 cases, respectively) (https://www.esot.org/news/latest-news/survey-sars-cov-2-and-liver-transplantation).

Worldwide data by TTS from 13 different countries reported 120 transplanted COVID-19-positive cases, including 23 (19.2%) deaths. However, when the data came from a severely hit area like the city of New York, 832-positive cases were reported, with 127 (15.3%) cases requiring intubation and 133 (16.0%) deaths (https://tts.org/11-tts/news/692-tts-coronavirus).

While the panel of experts from the AASLD stated that "post-transplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present), it seems too early to comment on the association with COVID-19; however, immunosuppressed patients are considered to be at higher risk for severe illness from COVID-19".[17]

The reported high fatality rate might be justified by several aspects, such as the higher median age and comorbidities of the transplanted population, besides the tendency to report the most severe cases respect to the uneventful ones.

Data on COVID-19 in transplanted patients are still sparse, and the opportunity to obtain a global picture is still limited. A more reliable estimate of how lethal SARS-CoV-2 is to transplant recipients could be obtained after matching them by age and comorbidities with the general population. Up to now, only a large study focused on pediatric transplantation has been published exploring the potential prevalence of COVID-19 in transplanted cases. In detail, the preliminary experience of the pediatric Transplant Center of the Hospital Papa Giovanni XXIII in Bergamo, Italy, located in the "red zone" of the Italian outbreak, was reported.[56] Interestingly, this large series based on 700 children did not report any case of clinical pulmonary disease and only three-positive cases. These data suggest that children, similarly to the general pediatric population, should develop a less aggressive course of COVID-19 also when immunosuppressed.[56]

**TABLE 3** Solid organ transplant patients experiencing SARS-CoV-2-related disease: details of COVID-19 management

| Author/Country/N | Ref | CoV-related treatment | Antibacterial treatment | PGGO | ARDS | ICU | Invasive ventilation | Death (d) |
|---|---|---|---|---|---|---|---|---|
| Alberici Italy N = 20 | [27] | HQC 95% LPV/r 79% DRV-RTV 21% Ster 55% TCZ 30% | Antibiotics 55%: cephalosporins 64% beta-lactams 36% fluoroquinolones 25% carbapenems 10% glycopeptides 5% | Yes: uni = 35% bi = 50% | NR | Yes 20% | Yes 10% | Yes 25% (day 15*) |
| Akalin USA N = 36 | [28] | HCQ 86% LRL 21% TCZ 7% High-dose Ster 7% | AZM 46% | Yes 96% | NR | NR | Yes 31% | Yes 28% |
| Banerjee UK N = 7 | [29] | None | None | NR | NR | No | No | No |
| | | None | Broad spectrum | Yes | Yes | Yes | Yes | Yes |
| | | OTV | Broad spectrum | Yes | Yes | Yes | Yes | Intubated |
| | | NR | Broad spectrum + TMP-SXT | NR | No | Yes | No | NR |
| | | NR | DOX TZP | NR | NR | Yes | NR | NR |
| | | NR | NR | NR | NR | No | No | No |
| | | NR | NR | Yes | NR | NR | NR | NR |
| Bhoori Italy N = 6 | [30] | NR | NR | Yes | Yes | Yes | Yes | Yes[3-12] |
| | | NR | NR | No | No | No | No | No |
| Billah USA N = 1 | [31] | NR | NR | Yes | Yes | Yes | Yes | NR |
| Boyarsky USA N = 148 | [32] | HCQ 78% TCZ 31% RDV 25% | AZM 47% | NR | NR | NR | 25% severely ill | NR |
| Bussalino Italy N = 1 | [33] | HCQ OTV | CPT | No | No | No | No | No |
| Chen China N = 1 | [34] | RBV IVIG | MXF | Yes | No | Yes | No | No |
| Columbia NY USA N = 15 | [35] | HCQ 27% HCQ + AZM 60% TCZ 7% | NR | Yes 50% | NR | NR | Yes 27% | Yes 7% |
| Fernández-Ruiz Spain N = 18 | [36] | LPV/r = 9 HCQ = 8 I FN-β = 3 IVIG = 2 TCZ = 1 | NR | Yes 72% | NR | Yes 11% | Yes 11% | Yes 28% |
| Gandolfini Italy N = 2 | [37] | HCQ LPV/r | NR | Yes | Yes | No | No | Yes[5] |
| | | DRV-COBI | NR | Yes | Yes | No | No | No |
| Guillen Spain N = 1 | [38] | LPV/r HCQ IFN-β | CPT MEM | Yes | Yes | Yes | Yes | Intubated |
| Hsu USA N = 1 | [39] | HCQ DRV-COBI | NR | Yes | Yes | No | No | No[14] |
| Huang China N = 2 | [40] | LPV/r IVIG | MXF CTR LZD MEM CAS | Yes | Yes | Yes | Yes | Yes[22] |
| | | OTV ECMO | MXF | Yes | Yes | Yes | Yes | Yes[40] |
| Huang China N = 1 | [41] | IFN-α UMV LPV/r ECMO | TZP CFP CAS | Yes | Yes | Yes | Yes | Yes[45] |
| Johnson USA N = 1 | [42] | HCQ | FEP AZM | Yes | No | NR | No | No |
| Kates USA N = 4 | [43] | HCQ AZM | CTR | Yes | No | No | No | No |
| | | Nil | NR | No | No | Yes | No | No |
| | | Nil | NR | No | No | No | No | No |
| | | Nil | NR | No | No | No | No | No |
| Li China N = 2 | [44] | RBV MXF GCV IVIG | LVX | Yes | No | No | No | No |
| | | NR | NR | No | No | No | No | No |
| Liu China N = 1 | [45] | OTV UMV LPV/r IFN-α IVIG | CFP | Yes | No | No | No | No |
| Maggi Italy N = 2 | [46] | NR | NR | NR | NR | NR | NR | No |
| | | NR | NR | NR | NR | NR | NR | Yes[30] |

(Continues)

**TABLE 3** (Continued)

| Author/Country/N | Ref | CoV-related treatment | Antibacterial treatment | PGGO | ARDS | ICU | Invasive ventilation | Death (d) |
|---|---|---|---|---|---|---|---|---|
| Marx France N = 1 | 47 | NR | NR | Yes | No | No | No | No |
| Mathies Germany N = 1 | 48 | HCQ GCV | TZP TMP-SXT | Yes | Yes | Yes | No | No |
| Meziyerh Netherlands N = 1 | 49 | HCQ LPV/r | CTR | Yes | Yes | Yes | Yes | No |
| Ning China N = 1 | 50 | LPV/r IVIG | MXF TMP-SXT | Yes | No | No | No | No |
| Qin China N = 1 | 51 | OTV h-GCSF IVIG | NR | Yes | No | NR | No | No |
| Seminari Italy N = 1 | 52 | None | CTR | Yes | No | No | No | No |
| Zhang China N = 5 | 53 | OTV UMV | NR | Yes | No | NR | No | No |
| | | OTV UMV | CFM | Yes | NR | NR | No | No |
| | | OTV UMV IVIG | NR | Yes | No | NR | No | No |
| | | OTV UMV | NR | Yes | No | NR | No | No |
| | | OTV UMV | NR | Yes | No | NR | No | No |
| Zhong China N = 2 | 54 | OTV | CFP | Yes | No | Yes | No | No |
| | | OTV UMV IFN-α IVIG | MXF | Yes | No | No | No | No |
| Zhu China N = 1 | 55 | UMV IFN-α IVIG | MXF BIPM | Yes | No | No | No | No |

*Median

Abbreviations: ARDS, acute respiratory distress syndrome; AZM, azithromycin; BIPM, biapenem; CAS, caspofungin; CFM, cefixime; CFP, cefoperazone-sulbactam; CPT, ceftaroline; CTR, Ceftriaxone; DOX, doxycycline; DRV-COBI, darunavir-cobicistat; DRV-RTV, darunavir/ritonavir; ECMO, extracorporeal membrane oxygenation; FEP, cefepime; GCV, ganciclovir; HCQ, hydroxychloroquine; h-GCSF, human granulocyte colony-stimulating factor; ICU, intensive care unit; IFN, interferon; IPM, imipenem; IVIG, intravenously injected immunoglobin; LPV/r, lopinavir-ritonavir; LRL, leronlimab; LVX, levofloxacin; LZD, linezolid; MEM, meropenem; MXF, moxifloxacin; not reported; OTV, oseltamivir; PGGO, patchy ground-glass opacity; RBV, ribavirin; RDV, remdesivir; Ref, reference; TCZ, tocilizumab; TMP-SXT, Trimethoprim-Sulfamethoxazole; TZP, piperacillin-tazobactam; umifenovir; UMV; VAN, vancomycin.

## 7 | CoV-RELATED DISEASE AND IMMUNOSUPPRESSION CHANGES IN TRANSPLANTED PATIENTS

Data on the modification of immunosuppressive regimens in transplanted patients experiencing the SARS-CoV-2 infection are reported in Table 2.[27-55]

Before infection, the most common baseline maintenance immunosuppression was CNI, MMF with or without steroids. In the 126 cases in which the post-COVID-19 immunosuppression therapy was detailed, the most common form of immunosuppression modification was the discontinuation of the antimetabolites MMF or azathioprine (n = 41, 32.5%), followed by the discontinuation of the entire immunosuppression regimen (n = 37, 29.4%), the discontinuation of the CNI (n = 17, 13.5%), and the dose reduction of all the immunosuppressive drugs (n = 10, 7.9%). Remarkably, 116/126 (92.1%) cases maintained or reintroduced steroids during the infection. In some cases, steroids were switched from oral to intravenous form following discontinuation or reduction of all the other drugs (n = 26/126, 20.6%).

From the data above, a divergence between clinical reality and societal recommendations emerges.

As an example, the discontinuation of azathioprine, MMF, or CNI seems more common than just the dose reduction that was suggested by the AASLD in cases of lymphopenia, fever, or worsening pneumonia caused by COVID-19.[17]

Similarly, in consensus-based guidance derived from individual information of 19 transplant societies, only the reduction—rather than the discontinuation—of immunosuppression was suggested (7/19 society consensus) in the absence of a recent history of transplant rejection.[24]

In the recent COVID-19 literature, complete immunosuppression withdrawal is often encountered, although this is probably magnified by the overreporting of severe COVID-19 cases. Expectedly, an even larger yet unreported group of patients with uneventful infections might maintain or lower their immunosuppression.

Cross-sectional studies are required to unfold real-life clinical practice with immunosuppression management. As of now, we can only observe that a general consent exists on a slight reduction of the immunosuppressive load in CoV-positive patients with moderate clinical status, while the reported clinical experiences show a trend toward a more aggressive immunosuppressive reduction in severe cases.

## 8 | FINAL CONSIDERATIONS

SARS-CoV2 can cause a fearsome disease evolving in ARDS, pulmonary fibrosis, and death. The role of the transplant physician is to correctly diagnose and manage the infected transplanted patient,

**TABLE 4** Considerations on immunosuppression (IS) in transplanted patients with COVID-19

| Considerations on IS management | | Ref. |
|---|---|---|
| #1 | Immunosuppressors (ie, steroids) may present more intense and prolonged virus shedding. | 7-9,11 |
| #2 | The reduced virus clearance can potentially increase the risk of transmission to contacts, also including healthcare workers. | 57 |
| #3 | Steroids should be carefully used in light of their potential benefits and harms. | 15 |
| #4 | Steroids should be prudently used in critically ill patients with COVID-19 pneumonia. | 15 |
| #5 | In transplanted patients regularly using steroids, their further use should be cautious. | 15,17 |
| #6 | Steroids dosage should be low-to-moderate (≤0.5-1 mg/kg per day of methylprednisolone or equivalent) and the duration should be short (≤7 d). | 15 |
| #7 | In vitro studies showed that calcineurin inhibitors or mycophenolic acid derivates reduce viral replication. | 18-23 |
| #8 | No clinical evidence exists on the potentially positive impact of calcineurin inhibitors or mycophenolic acid derivates in transplanted patients with COVID-19. | - |
| #9 | In case of moderate illness, only an IS reduction should be considered. | 17,24 |
| #10 | In severely ill patients with high risk of ARDS and bacterial superinfections, IS suspension apart low-dose steroids should be considered. | 25-55 |
| #11 | No studies exist on the potential interaction between immunosuppressors and the different antiviral drugs: therefore, immunosuppressant plasma levels should be often checked. | 58 |
| #12 | Interferon-beta and (hydroxy) chloroquine should be cautiously adopted in transplanted patients for the risk of rejection and toxicity. | 59,60 |
| #13 | Consult the drug interactions documents on the possible interactions using experimental COVID-19 therapies. | 17 |
| #14 | Monitor new studies of antiviral and immunomodulatory approaches for COVID-19 treatment. | 17 |

Abbreviations: ARDS, Acute respiratory distress syndrome; COVID-19, Coronavirus disease-19; IS, immunosuppression.

thereby optimizing clinical management. It is not clear if transplanted cases present a higher risk of contracting the infection, but data show that transplant recipients are at higher risk for severe COVID-19 than the average population.

Unfortunately, due to the lack of knowledge concerning COVID-19 in transplanted patients, it is not possible to provide evidence-based recommendations regarding the use of immunosuppressants. The observed results in the present study mainly draw on extrapolation from scarce data on other viral diseases, in vitro data, case reports, small series, and international guidelines based on sound clinical practice and common sense. However, we attempted to summarize some considerations extrapolated from published data (Table 4). The limitation of our work resides in the evolving body of literature on COVID-19 and transplantation, which is released daily and precludes a systematic approach in the review process. Besides, the heterogeneity of the reported cases and the limited information provided within the articles we analyzed, renders any conclusions speculative and should not be intended as guidance on patient management. Nevertheless, we intended to provide transplant physicians with a useful snapshot of the available reports on the topic and to frame this clinical data with the knowledge around previous coronavirus infections in immunocompromised and transplanted patients.

The reported literature shows that CoV-positive transplanted patients treated with immunosuppressants such as steroids may present more intense and prolonged virus shedding, thereby increasing potentially the risk of transmission to contacts, including healthcare workers.[7-9,11,57]

On the other side, the use of steroids in the treatment of ARDS showed controversial results, and moderate use is suggested. The cautious approach proposed by Shang et al seems reasonable. Steroid use should be (a) carefully weighed case by case in light of the potential benefits and harms; (b) prudently administered in critically ill patients with COVID-19 pneumonia; (c) as well as in patients regularly using steroids (such as transplanted patients), further use of steroids should be cautious; and, (d) the dosage should be low-to-moderate (≤0.5-1 mg/kg/d methylprednisolone or equivalent), and the duration should be short (≤7 days).[15]

As for the other immunosuppressive drugs, no clinical shreds of evidence exist concerning their impact in transplanted COVID-19 patients. Theoretically, in vitro studies showed that the use of CNI or mycophenolic acid might be a strategy to reduce viral replication.[17-23] Since no clinical studies exist on this aspect, caution is recommended when managing immunosuppressors in COVID-19-positive patients. In the presence of moderate illness, only a reduction of the immunosuppressive load should be considered.[17,24] In severely ill patients with a high risk of ARDS and potential bacterial superinfections, several small clinical shreds of evidence reported the decision to discontinue the immunosuppression drugs.[25-55]

No studies exist on the potential interaction between immunosuppressants and the different antiviral drugs, including remdesivir, lopinavir/ritonavir, darunavir-cobicistat, interferon–beta, and (hydroxy)chloroquine used in the treatment of COVID-19.[58] However, increased trough levels of tacrolimus have been observed after patients received antiviral treatment, with subsequent nephrotoxicity. Consequently, it is essential to measure frequently the

immunosuppressant plasma levels with the intent to prevent over-immunosuppression and to cautiously adopt or even avoid drugs such as interferon-beta and (hydroxy)chloroquine in transplanted patients which could lead to rejection or toxicity.[59,60] In this context, it should be important to consult the University of Liverpool Drug Interactions Group document on the possible interactions using experimental COVID-19 Therapies (https://www.covid19-druginteractions.org), and to monitor the new studies of antiviral and immunomodulatory approaches for the treatment of COVID-19.[17]

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare about the present study.

## AUTHORS CONTRIBUTIONS

QL, GS, and JL were responsible for the conception, design, analysis, and writing of the study; QL, GS, GB, and DG were involved with the collection and interpretation of data; MR and JL participated in data management, review, and editing of the manuscript.

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