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Review

COVID-19 in Patients with Solid Organ Transplantation: A Systematic Review

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Abstract: The novel coronavirus, SARS-CoV-2, is causing a pandemic of unknown precedent, with huge healthcare challenges and worldwide disruptions to economic and social life. Lung transplant recipients and other solid organ transplant (SOT) recipients are immunosuppressed, and therefore are generally considered at an increased risk for severe infections. Given the current gap in knowledge and evidence regarding the best management of these patients, we conducted a systematic review of studies on SARS-CoV-2 infections and Coronavirus Disease 2019 (COVID-19) in SOT recipients, to evaluate the association between immunosuppression in these patients, SARS-CoV-2 infection and COVID-19 outcomes. The focus was the severity of the disease, the need for mechanical ventilation and intensive care unit (ICU) admissions, and rate of death. The literature search was conducted repeatedly between 16 March and 8 April 2020. We searched original papers, observational studies, case reports, and meta-analyses published between 2019 and 2020 using two databases (PubMed, Google Scholar) with the search terms: [transplant OR immunosuppression] AND [COVID-19 OR SARS-CoV-2]. Further inclusion criteria were publications in English, French, German and Italian, and reference to humans. We also searched the reference lists of the studies encountered. From an initial search of PubMed and Google Scholar, 19 potential articles were retrieved, of which 14 were excluded after full-text screening (not being case reports or case series), leaving 5 studies for inclusion. No further studies were identified from the bibliographies of retrieved articles. Based on the limited research, no firm conclusions can be made concerning SOT recipients, but the current evidence suggests that immunosuppression is most likely associated with a better outcome of SARS-CoV-2 infection and COVID-19 because it prevents hyperinflammation (cytokine storm) in this particular population. There is a need for further research that would allow results to be adjusted for other factors potentially impacting COVID-19 severity and outcome.

Keywords: SARS-CoV-2; coronavirus; immunosuppression; tacrolimus; corticosteroids; mycophenolate mofetil; hyperinflammation; cytokine storm; pandemic; transplantation

1. Introduction

The emergence of the novel coronavirus, which started in the last quarter of 2019 in Wuhan (China), and its rapid spread around the world, have caused a pandemic of global concern and impact [1]. The virus was first termed 2019-nCOV, and the International Committee on Taxonomy of Viruses subsequently named it "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2).

The novel coronavirus has a presumptive zoonotic origin [2]. According to the Emergency Committee of the World Health Organization (WHO), the 2019-nCOV was declared a public health

emergency of international concern (PHEIC) on 30 January 2020 [3]. The WHO named the disease caused by SARS-CoV-2 "COVID-19". As yet, effective treatment against SARS-CoV-2 is absent.

1.1. Known Coronaviruses with Fairly Benign Outcomes

Coronaviruses infecting humans are not new. The wide range of possible hosts includes birds, pets, bats, farm animals and camels. Currently there are seven coronavirus species causing disease in humans. In four of these, called 229E, OC43, NL63 and HKU1, respiratory symptoms predominantly consist of self-limiting common cold symptoms, causing a respiratory or gastrointestinal disease. Infections with the strain 229E can be associated with fever and cough in 10−20% of cases. The illness usually lasts between 2 and 18 days [2]. Patients affected by the strain OC43 have the same symptoms as those affected by the 229E strain. Infections with NL63, a strain known since 2004 and initially described in the Netherlands, cause typically mild symptoms, whereby it primarily is observed in young children, elderly and immunocompromised patients with prior respiratory illnesses. In children it can also cause obstructive laryngitis (croup) [4]. However, a subtype of NL63 has been associated with severe lower respiratory tract infection in hospitalized children in China [5]. The HKU1 strain was discovered in 2005 in Hong Kong, causing relatively mild respiratory symptoms in children, but it is also associated with a high incidence of seizures and has also been found in a patient with meningitis [4,6,7]. In contrast to the benign outcomes in the general population, in lung transplant recipients these viruses can cause acute febrile illnesses, and may even persist for up to several months in some individuals, making concurrent infection with another virus difficult to interpret [8]. In lung transplant recipients, a viral respiratory tract infection (VRTI) is associated with chronic lung allograft dysfunction (CLAD). In the first year after lung transplantation, coronavirus in particular is associated with increased risk of CLAD development [9]. In a study by Magnusson, in a total of 125 lung transplant recipients with VRTI, 19.2% (n = 21) had a coronavirus infection. The coronavirus subspecies were OC43 in 7.2% (n = 9), 229E in 5.6% (n = 7), NL63 in 3.2% (n = 4) and HKU1 in 0.8% (n = 1) [9]. Another study showed that coronaviruses have an important role among patients with underlying conditions and in transplanted patients [10]. In healthy children, human coronaviruses were detected in 3.3% (n = 11), in healthy adults in 12% (n = 6), in health care workers in 12.8% (n = 86), in patients after renal transplantation in 20.3% (n = 30), in children with heart diseases in 24.7% (n = 44) and in patients after stem cell transplantation in 24.3% (n = 44) [10].

1.2. The Highly Pathogenic Coronaviruses

The other three coronavirus species are zoonotic in origin and have been associated with severe, life-threatening respiratory disease outbreaks. The first was Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), leading to an outbreak in 2002 and 2003 in Guangdong Province (China). It was initiated by a zoonotic transmission (likely from bats via palm civets), and infected 8098 people, leading to an overall case fatality rate of 11% [11]. This was followed by the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks in 2012 (Saudi Arabia) and 2015 (South Korea), probably originating from bats via dromedary camels. Unlike SARS, the infection with MERS-CoV is generally mild in healthy individuals, but very severe in patients with underlying comorbidities, such as chronic lung diseases, diabetes, renal failure and a weakened immune system. It infected 2994 people, with a case fatality rate of 34% [12]. The third zoonotic coronavirus is the recent 2019 novel coronavirus SARS-CoV-2, which originated in Wuhan (South China). The recent outbreak of the SARS-CoV-2 has been linked to the Huanan Seafood Wholesale Market in Wuhan. This market sold a variety of both live and dead animals of wild and domesticated origin in over one thousand stalls. There is some debate about whether this market is the true origin of the outbreak, but it certainly was one area of early transmission in the 2020 pandemic.

1.3. Route of Transmission

Based on our current knowledge, spreading of the SARS-CoV-2 occurs from person to person via respiratory droplets (defined as particles > 5 µm). Risk factors are close contact (≤2 m), especially over a prolonged time (generally considered to be >15 min), and direct contact with infectious secretions like sputum or blood [13]. A fecal−oral transmission appears likely but has not been proven yet [14]. Not only can SARS-CoV-2 be found in feces, but also stool samples can remain positive even when samples from the respiratory tract have become negative [15].

The gastrointestinal symptoms in some patients with COVID-19 may be explained by the extended persistence and shedding in the gastrointestinal tract.

Infection with SARS-CoV-2 can lead to a disease called COVID-19 that predominantly affects the lungs. The impact of COVID-19 in immunocompromised patients after solid organ transplantation (SOT) is largely unknown, as only a small number of such infections have occurred so far, and detailed reports are still awaited.

1.4. Severity Stages of COVID-19

COVID-19 can have various stages of severity. Siddiqi et al. proposed three stages of COVID-19 severity [16] (Figure 1):

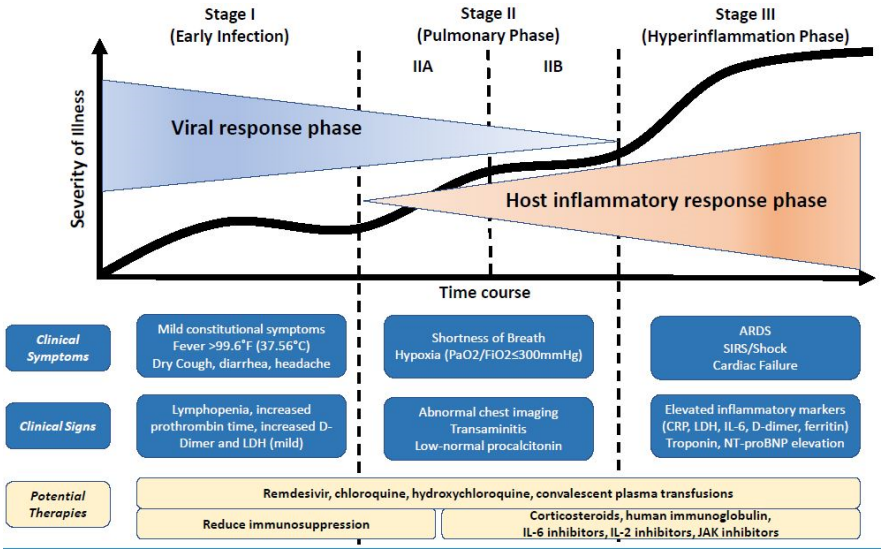

Figure 1. Classification of COVID-19 Disease States and Potential Therapeutic Targets. Legend: The figure shows three escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome; CRP = C-reactive protein; IL = Interleukin; JAK = Janus Kinase; LDH = Lactate Dehydrogenase; SIRS = Systemic inflammatory response syndrome. (From: Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020 [in press], DOI:https://doi.org/10.1016/j.healun.2020.03.012).

Stage I (early infection) can include mild constitutional symptoms—fever, dry cough, diarrhea, headache—with laboratory examination revealing lymphocytopenia, increased prothrombin time, increased D-dimer and mild Lactate Dehydrogenase (LDH) elevation.

Stage II (pulmonary phase) can be subdivided into IIa (without hypoxia) and IIb (with hypoxia, defined as a PaO_2/FiO_2 of < 300 mmHg). In Stage II disease, patients develop a viral pneumonia, with cough, fever and possibly hypoxia. Radiologic imaging shows bilateral infiltrates or ground-glass opacities. Laboratory tests reveal increasing lymphocytopenia, along with elevated transaminases. At this stage, most patients with COVID-19 should be hospitalized.

Stage III (systemic hyperinflammation) is characterized by Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS)/shock, and/or cardiac failure. In the laboratory examination there are elevated inflammatory markers (C-reactive Protein, LDH, Interleukin-6, D-dimer, ferritin), and an elevation of troponin and N-Terminal-pro-Brain Natriuretic Peptide (NT-proBNP).

1.5. Diagnosis

According to the guidelines of the International Society of Heart and Lung Transplantation (ISHLT) concerning patients with cardiothoracic transplant, routine testing of asymptomatic patients is not recommended [17]. An asymptomatic patient who has been in contact with a confirmed case of COVID-19 should be advised to undergo home quarantine for 2 weeks, and testing for SARS-CoV-2 is only indicated if symptoms occur (or otherwise as per local public health guidelines). Testing for SARS-CoV-2 in patients with symptoms of COVID-19 (fever, cough, headaches, myalgia, fatigue, nasal congestion, sudden anosmia, diarrhea, etc.) should be treated like any other patient considered at increased risk of developing severe disease, as per local guidelines [17].

A real-time polymerase chain reaction (RT-PCR), or sequencing of respiratory or blood samples using "primers" based on the viral RNA sequence, indicates whether a person is currently infected. In a study on detection of SARS-CoV-2 in different types of specimens from 205 patients, the virus was detected in 93% (n = 14) of patients where bronchoalveolar lavage fluid was sampled, in 72% (n = 75) of sputum samples, in 63% (n = 5) of nasal swabs, in 46% (n = 6) of bronchoscopic brush biopsies, and in 32% (n = 126) of pharyngeal swabs. Further, in feces specimens, the virus was detected in 29% of cases (n = 44). In blood, SARS-CoV-2 could be detected in only 1% (n = 3), whereas in none of the patients could the virus be detected in urine [18]. Blood samples should be stored for subsequent analysis, for example for antibody testing. Recently, in collaboration between the U.S. Department of Health and Human Services, the U.S. Department of Defense, and the company Cepheid, a new COVID-19 molecular diagnostic test, allowing SARS-CoV-2 detection within 45 min, has been approved by the U.S. Food and Drug Administration (FDA) for point-of-care detection in emergency use for COVID-19. A further benefit of this rapid diagnostic test is that it only requires one minute hands-on time to perform it, reducing the exposure time of the laboratory personnel to potentially virus-containing samples. However, the question remains unanswered as to how this test compares to the widely used RT-PCR test. There have been concerns related to potential false negative results.

Serologic diagnosis by detection of specific antibodies (immunoglobulin M, immunoglobulin G) is currently being introduced. Timelines for the appearance and persistence of these immunoglobulins are currently not well established.

In this paper, we review COVID-19 in solid organ transplant (SOT) recipients, most of whom are under long-term dual- or triple-drug immunosuppressive therapy.

2. Methods

The literature search was conducted repeatedly between 16 March and 8 April 2020. We searched original papers, observational studies, case reports and meta-analyses published between 2019 and 2020, using two databases (PubMed, Google Scholar) with the search terms: [transplant OR immunosuppression] AND [COVID-19 OR SARS-CoV-2]. Further inclusion criteria were publications in English, French, German and Italian, and reference to humans. We also searched the reference lists of the studies encountered.

3. Results

From an initial search of PubMed and Google Scholar, 19 potential articles were retrieved, of which 14 were excluded after full-text screening (not being case reports or case series), leaving 5 studies for inclusion. No further studies were identified from the bibliographies of retrieved articles.

Table 1. Main references of original papers and case reports (excluding reviews, meta-analyses or commentaries).

Author, Ref. and Date	Solid Organ Transplanted, Year of Transplant	Age (y) Sex (m/f)	IS Rx	Symptoms	Temp SpO_2 CRP CT Chest	Severity Stage (Siddiqi)	Treatment	Outcome
Steinack et al. [19]	Lung, 2019	55 f	Tac MMF Pred	Nausea Vomiting Diarrhea Dry cough Rhinorrhea	38.9 96% 77 mg/L 3 nodular lesions	IIA	piperacillin/tazobactam iv	survived hospitalzation 12 days
Li et al. [20]	Heart, 2003	51 m	Tac MMF	intermittent fever chills fatigue poor appetite diarrhea	38.5 99%–> 75% 18.6 mg/L GGO (bilat.)	IIA –> IIB	levofloxacin iv ribavirin iv moxifloxacin iv ganciclovir iv IVIG methylprednisolone iv moxifloxacin po umifenovir Tac and MMF stopped from day 7–13	survived, hospitalization 27 days, no mechanical ventilation or ECMO, CT at discharge improved (residual lesions).
Li et al. [20]	Heart, 2017	43 m	Tac MMF	fever (2 days) fatigue poor appetite	38.5 normal SpO_2? 13.4 mg/L GGO (bilat.)	IIA	ceftriaxone iv ganciclovir iv moxifloxacin po umifenovir	survived, hospitalization 11 days, no mechanical ventilation or ECMO
Zhu L et al. [21]	Kidney, 2008	52 m	Tac MMF Pred	fatigue dyspnea chest pain tightness nausea loss of appetite abdominal pain dry cough fever headache	38.9 96% 30.2 mg/L GGO (bilat.)	IIA	umifenovir methylprednisolone interferon-α inh. IVIG Biapenem iv pantoprazole Tac stopped from day 6–11, reintroduced with 50% reduction for 7 days, followed by normal doses MMF stopped from day 6–11, reintroduced by normal dose after 12 days pred stopped during hospitalization	survived, hospitalization 12 days, no mechanical ventilation or ECMO

Table 1. *Cont.*

Author, Ref. and Date	Solid Organ Transplanted, Year of Transplant	Age (y) Sex (m/f)	IS Rx	Symptoms	Temp SpO_2 CRP CT Chest	Severity Stage (Siddiqi)	Treatment	Outcome
Guillen E et al. [22]	Kidney, 2016	50 m	Tac Everol Pred	fever vomiting	37.4 98% 13.2 mL/L unilateral –> bilat. infiltrate	IIA–> IIB	ceftriaxone azithromycin lopinavir/ritonavir HCQ TAC and everol temporarily stopped due to interactions interferon-β intubation and MV	
Qin J et al. [23]	Liver, 2020	37 m	Tac Pred	unknown	Temp, SpO_2 and CRP unknown GGO	IIB	Tac and Pred maintained, gradually titrated to lower doses HFOT Oseltamivir rh-GCSF IVIG	survived, hospitalization 2 months (including liver transplantation)
Gandolfini I, et al. [24]	Kidney, 2010	75 m	Tac Pred MMF	Fever Cough Myalgia Dyspnea	38.0 SpO_2 and CRP unknown GGO	IIB	NIV HCQ Lopinavir-ritonavir or darunavir-cobicistat	died
Gandolfini I, et al. [24]	Kidney, 2019	52 f	Tac Pred MMF	Fever Cough Myalgia Dyspnea	39.0 SpO_2 and CRP unknown GGO	IIB	NIV HCQ Lopinavir-ritonavir or darunavir-cobicistat Colchicine	alive

3.1. Lung Transplant Recipients

Steinack et al. reported a 55-year-old woman who underwent a bilateral lung transplantation 5 months prior to infection. The lady was under therapy with tacrolimus, mycophenolate mofefil and prednisolone (Table 1) [19]. The patient presented with gastrointestinal symptoms (nausea, vomiting, diarrhea) and only minor respiratory symptoms (dry cough and rhinorrhea). Initially, she had fever and normal oxygen saturation breathing room air. Stool specimens detected a Norovirus infection, and virus PCR testing of the nasal swab returned positive for SARS-CoV-2. There were only minimal consolidations on chest computed tomography (CT) imaging, without any associated ground-glass opacities. She recovered on empiric intravenous antibiotic treatment without the use of additional antiviral agents, whilst continuing preexisting Cytomegalovirus (CMV)-prophylaxis with valganciclovir. There were no signs of allograft dysfunction in the 6-week follow-up.

3.2. Renal Transplant Recipients

There are three case reports describing a COVID-19 with stages IIA and IIB (Table 1) [21,22,24]. In the case report by Guillen et al., the first patient was a 50-year-old man under tacrolimus, everolimus and prednisone therapy [22]. He presented to the hospital with fever and vomiting, without other symptoms. After 5 days, the patient, who initially was sent home, returned to the emergency department with persistent fever and cough, but without gastrointestinal symptoms. At that time, he was afebrile and had a normal oxygen saturation. Because of a unilateral infiltrate on chest X-ray (CXR), a community-acquired pneumonia was considered. However, he tested positive on naso- and oropharyngeal swabs for SARS-CoV-2. He was treated with lopinavir/ritonavir, but worsened clinically with disease progression on CXR showing bilateral infiltrates, requiring intubation with mechanical ventilation. The final outcome of the patient has not yet been communicated.

Zhu et al. [21] described a 52-year-old man on immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisone. He presented with fatigue, dyspnea, chest tightness, chest pain, nausea, loss of appetite, intermittent abdominal pain and occasional dry cough. He developed fever and the chest CT showed bilateral ground-glass opacities, suggesting the presence of COVID-19 pneumonia. Immunosuppression was completely stopped, and treatment with methylprednisolone (40 mg daily, intravenously), intravenous immunoglobulins (5 g on the first day and 10 g/day for the next 11 days), biapenem, pantoprazole, and Interferon (IFN)-α (5 million units daily by atomization inhalation) was started. A follow-up chest CT showed massive improvement later, and the patient was finally discharged from hospital.

Gandolfini et al. [24] described two stage IIB COVID-19 renal transplant cases requiring non-invasive ventilation. Both patients were on tacrolimus, steroids and mycophenolate mofetil, presenting with fever and dyspnea on admission, with CT showing bilateral ground-glass opacities. The first patient developed abrupt worsening of his respiratory conditions and died 5 days after admission to the hospital, before he could be intubated. The second patient was stabilized and treated with colchicine after initially receiving retroviral therapy and hydroxychloroquine.

3.3. Liver Transplant Recipients

In liver transplant recipients, only one case report with COVID-19 stage IIB has been published (Table 1) [23]. A 37-year-old man underwent a liver transplant 3 months previously. He was under immunosuppressive therapy with tacrolimus and glucocorticoids. Two days after transplantation, he had a persistent fever and chest CT showed a minor pleural effusion. His sputum showed gram-positive cocci and gram-negative bacilli. After 9 days, his chest CT was repeated and, due to the COVID-19 outbreak, he was sampled for SARS-CoV-2 and found positive. He required high-flow oxygen therapy, and additionally tacrolimus and glucocorticoids were gradually titrated to lower doses. After 24 days, his fever subsided, and tacrolimus was increased due to acute cellular rejection. The patient was discharged without any signs of multisystem organ failure during hospitalization.

3.4. Heart Transplant Recipients

Recently, two heart transplant recipients from China with COVID-19 have been reported: one patient with a moderately severe (stage IIB) and another with a mild (stage IIA) presentation (Table 1) [20]. The first patient was a 51-year-old man on maintenance immunosuppressive therapy with tacrolimus and mycophenolate mofetil. He initially presented with fever, chills, fatigue and poor appetite, as well as diarrhea. He had a normal oxygen saturation initially, but then his clinical condition worsened, and his saturation decreased to 75% without supplemental oxygen. This was improved after giving oxygen via a face-mask. He was treated with intravenous human gammaglobulin (10 g/day) and methylprednisolone (80 mg/day) for 5 days, while immunosuppression was stopped. The initial ground-glass opacities in the chest CT showed significant improvement after therapy, and the patient was discharged from the hospital.

The second patient was a 43-year-old man with tacrolimus and mycophenolate mofetil maintenance immunosuppression, who was admitted having suffered from fever for 2 days with fairly discrete lung lesions on his chest CT (stage IIA). His clinical situation deteriorated, and he suffered from severe fatigue and poor appetite. There were no further complications and he could be discharged from the hospital.

3.5. Consequences for the Pre- and Post-Transplantation Practice

3.5.1. What Is New in the COVID-19 Pandemic?

Viral diseases in the past have motivated researchers to generate algorithms for donor screening, in order to prevent the use of organs from potentially infected donors, and also to improve recipient management, in order to reduce the chances of viral transmission and disease among recipients [25]. Some of the emerging viruses in the past (SARS-CoV, MERS, etc.) were only limited to a certain geographic area, thus not severely hampering the transplantation/donation procedure as a whole. The current COVID-19 pandemic is of unprecedented magnitude. The virus is highly contagious, crossing borders all over the world. There are over 3,500,000 confirmed cases and over 245,000 deaths, affecting 206 countries [26], and probably many more undiagnosed people with COVID-19. Unfortunately, the widespread occurrence of the virus has a great impact on SOT, requiring preventive and possibly therapeutic measures.

3.5.2. Restrictions Concerning Donors, Recipients and Transplantation Centers

Not only does the pandemic restrict the number of potential organs available due to infected donors, but it may also affect recipients on the waiting list or just before transplantation. Donor screening for the presence of the SARS-CoV-2 virus or evidence of disease (COVID-19) is highly recommended, which may lead to possible delays in organ procurement and organ transplantation, depending on testing availabilities. In addition, the large number of COVID-19 patients requiring specialist care, including intensive care unit (ICU) resources, certainly competes with the efforts to transplant severely ill patients in order to enable survival and increase quality of life. The pandemic is therefore restricting the capacity for transplantation in many hospitals. This is also due to the transformation of many general or specialized intensive care units (ICUs) into specialized COVID-19 ICUs with strict isolation measures, and also due to shortages of health care workers relating to COVID-19 care requirements. In addition to the scarcity of ventilator capacity in ICUs, many hospitals have shut down their routine outpatient checkups in order to prevent further spread of the infection, resulting in impaired or absent capacity for evaluating patients for possible SOT. These factors will decrease both the number of potential donors and SOT recipients all over the world. On the other hand, there may be hospitals still evaluating candidates and performing transplantation procedures, thanks to sufficient ICU bed availability. Depending on the resources available, the waiting list mortality may suffer under these circumstances. In these centers, donor organ procurement and transplantation can

possibly be increased, when other centers decide to shut down their SOT programs of solid organ transplantations due to the requirements for COVID-19 care.

3.5.3. Shutdown in Phases: Different Consequences for Different Organs

A phased approach to new transplant activity during the COVID-19 pandemic has been proposed by Kumar et al. [25]. In this article, a reduction of 25%, 50% or 75% in transplant activity depends on the risk tolerance, hospital capacity and degree of virus activity in the jurisdiction [25]. This has different consequences for each type of organ. For example, a 25% reduction in transplant activity corresponds to priority level "elective", which means that there will be no living donor kidney transplantation, but non-urgent lung transplantation activity will be continued. A 100% reduction of the health system occurs if facilities are overwhelmed with COVID-19 patients, with no ICU capacity. In that situation, severe shortages of health care personnel lead to a halt of all living and deceased donor transplant activity.

The same authors also propose a classification of 25%, 50%, 75% and 100% reduction in ambulatory transplant checkups, with the corresponding levels of medical service at the transplant center.

3.5.4. Risks for Recipients

To the best of our knowledge, until now there have been no cases of donor-to-recipient transmission of SARS-CoV-2. On the other hand, recipients run the risk of nosocomial SARS-CoV-2 infections during the pandemic. Asymptomatic patients infected with SARS-CoV-2 can spread the virus. It is currently unknown whether asymptomatic individuals are only asymptomatic initially after contracting the infection, or if they remain asymptomatic throughout the course of the SARS-CoV-2 infection. In spite of the asymptomatic carrier state, these individuals may transmit the virus, although the exact mechanism of acquiring and transmitting the virus requires further study [27,28]. Even in a convalescent patient, a high sputum viral load has been demonstrated, raising concerns about prolonged viral shedding of SARS-CoV-2 after recovery [28].

3.5.5. Risks for Health Care Workers in General

In Italy, health care workers with COVID-19 were reported to be 8.9% of all COVID-19 patients (2026 of 22512 people, respectively). In comparison, the 2002–2003 SARS epidemic led to 8422 probable cases, with 916 deaths in 29 countries, affecting health care workers in approximately 30% of all SARS infections. As has been demonstrated for SARS, peak viral loads were reached at 12–14 days of illness, when patients were probably hospitalized, explaining the relatively high number (n = 174, 17%) of health care workers testing positive for the SARS virus. Another aspect that merits more attention is the huge amount of psychological stress among medical and paramedical team members, associated with risks of burnout, insomnia, anxiety, distress, depression or post-traumatic stress disorder (PTSD) [29,30]. This aspect, however, is not the focus of this review, also due to the currently limited data relating to this issue.

3.5.6. Health Care Workers with Pregnancy

The elevated risk of COVID-19 in health care workers may also involve pregnant transplant team members. Data on pregnant COVID-19 patients are very limited. The clinical presentation in pregnant women was similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia [25]. Currently, there is no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy [31]. Another study with 15 pregnant patients with COVID-19 pneumonia showed no worse clinical outcome in terms of CT imaging features of COVID-19 pneumonia. Nevertheless, these patients had only a mild type of COVID-19 pneumonia. There was no neonatal asphyxia, neonatal death, stillbirth or abortion, but 4/15 patients still were pregnant at the end of the study, and the final outcome of this population

has not been reported yet [32]. However, it is noteworthy that the maternal immune system in early pregnancy is very sensitive, and for the fetus this is an important stage of organ development [33].

In the H1N1 2009 influenza viral infections, the SARS outbreak in 2003, and the MERS outbreak in 2012, there were high incidences of maternal and infant complications, such as spontaneous abortion, premature delivery, intrauterine growth retardation, tracheal intubation, admission to intensive care unit, renal failure and disseminated intravascular coagulation (DIC) [33–36]. In the SARS outbreak, 57% of the women during the first trimester had spontaneous abortions, likely a result of the hypoxia during SARS-related acute respiratory distress [36].

In a case-control study to determine the effects of SARS on pregnancy, comparing ten hospitalized pregnant and 40 hospitalized non-pregnant women with the SARS infection in Hong Kong, the maternal mortality rate with SARS was 30%, compared to 0% in the non-pregnant group [37]. In pregnant women with SARS-CoV during the 2002–2003 epidemic, there were no cases of vertical transmission of the virus documented [11].

3.5.7. Health Care Workers in Transplant Teams

Any transplant team member with symptoms of a viral infection should undergo the appropriate testing, and avoid exposure to patients as long as symptoms persist or while the test result is pending. For transplant team members, there are also risks during exposure to transplant recipients potentially spreading viral infections with larger quantities of virus (super-shedders or super-spreaders) and/or prolonged viral shedding [38].

4. Discussion

We reviewed the currently available evidence on various aspects of SARS-CoV-2 infections and COVID-19, relating to SOT recipients and the transplant teams involved. Some special aspects need to be discussed.

4.1. The Potentially Protective Effect of Immunosuppression Relating to COVID-19 Stage III, a Hypothesis Based on Preliminary Observations in SOT

With respect to the COVID-19 case fatality in patients with chronic immunosuppression after SOT, both a higher incidence of disease and mortality could be expected. Surprisingly, this has not been the case so far. Until mid April, only seven documented cases in patients with SOT had been reported, whereas SARS-CoV-2 had by then resulted in more than 2,000,000 infections worldwide. In Italy, patients with COVID-19 (irrespective of clinical stage) required ICU admission in 12% of the total SARS-CoV-2 positive cases presenting with any kind of symptom and sampled for virus material, and 16% of all hospitalized patients [39]. In China, case fatality was 49.0% in critical cases (1023 of 2087), and in Italian patients it has been reported to be high as 7.2%, although final numbers from the ongoing coronavirus crisis are still pending [39].

One possible explanation for these unexpectedly low numbers could be that immunosuppression in SOT patients protects against the dramatic elevation of pro-inflammatory cells in the presence of COVID-19. It possibly mitigates the hyperinflammation (“cytokine storm”) that can be observed in immunocompetent patients with COVID-19 Stage III. There is some evidence that this is true for the calcineurin inhibitor tacrolimus (see below). Secondly, a cytopathic effect due to the virus could play an important role. Viruses can kill the human cells in which they reproduce, leading to cellular damage in the infected organs. The question of whether immunosuppressive therapy also can mitigate the viral cytopathic effect remains unanswered. Reports on autopsy in COVID-19 patients are extremely rare. Tian et al. described the pathologic findings in two COVID-19 patients, showing edema and prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multinucleated giant cells. Reactive alveolar epithelial hyperplasia and fibroblastic proliferation (fibroblast plugs) is indicative of early organization [40].

The mechanism of a possible beneficial effect of immunosuppressive therapy remains unclear. One paradigm could be the effect of immunosuppressive therapy on both the innate and adaptive immunity to SARS-CoV-2. The innate immune response includes cells such as IL-1, -2, -3, -6, TNF-α and IFN-γ, trying to protect the human cells from infection and to eliminate the virus, occurring well before the adaptive immunity becomes activated. The adaptive immunity has two major divisions, which are the antiviral B-cell (antibody mediated) and T-cell immune response. The antibody-mediated response binds to free viral particles, in order to block infection of the host cells. This part of the immune response, however, has more importance in preventing reinfection, which is currently the focus in developing vaccines against SARS-CoV-2. In contrast, the T-cell division of the adaptive immunity is much more important for resolution of the virus than the B-cell response. T-cells are needed for recognizing and destroying SARS-CoV-2 infected cells and the coordination of the whole machinery of the inflammatory response. An overshoot of this inflammatory response could lead to organ damage (cytokine storm, hyperinflammation).

In most patients with SOT, the maintenance immunosuppression includes calcineurin inhibitors (CNIs, namely tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate mofetil (MMF) or azathioprine) and low-dose corticosteroids (prednisone or prednisolone) as maintenance therapy.

The CNIs impair upregulation of (among others) interleukin (IL)-2, thereby reducing the proliferation, maturation and survival of T-cells, impairing an effective immune response. They also inhibit IL-4, TNF-α and IFN-γ. Corticosteroids also reduce the expression of many molecules that are needed in the immune response, such as IL-1, -2, -3, -6, TNF-α and IFN-γ. The antiproliferative agents diminish the clonal expansion of the alloreactive T-cells.

In this way, a cytokine storm could possibly be prevented in SOT patients. Therefore, immunosuppression is probably not a risk factor, but rather beneficial in this population, although the number of observations is very low, not allowing definitive conclusions yet. Even in patients with a lung transplantation, who generally have a more profound immunosuppressive therapy compared to patients with other SOT, a higher risk of incidence and severity of COVID-19 has not been observed so far. Moreover, in the described cases, none of the patients had signs of a major acute or chronic allograft dysfunction, another known complication of respiratory viral infections, particularly in lung transplant recipients. On the other hand, by blocking the above-mentioned important components of the antiviral innate immune response, one would expect the incidence (not severity) of (mild) COVID-19 to be increased, or at least be equal to that among immunocompetent individuals. On the contrary, in the medical literature there is a surprisingly low number of case reports on SOT patients with COVID-19. This could be an under-reported group of patients, or the low number may be related to the fact that these patients have been aware of their susceptibility to infections since being transplanted, and thus act more prudently in the context of the pandemic than the non-transplanted population for whom these measures are largely new and not yet routine behavior. However, more studies concerning these questions and a longer follow-up are needed to draw more firm conclusions concerning these aspects of the pandemic.

What do we learn from studies in other coronaviruses? As seen in MERS, there is a potential role for tacrolimus [41]. One case report described two renal transplant recipients who tested positive for MERS CoV. The patient under tacrolimus had a full recovery, whereas the other patient, who was not on this treatment, did not survive the infection [42]. In vitro, in studies of the pathways of the viral replication of coronavirus, tacrolimus effectively inhibited the viral replication of SARS-CoV, coronavirus NL63 and 229E [43]. This was confirmed with a tacrolimus derivative in another laboratory study [44]. Although these studies are not specific to COVID-19, evaluation of tacrolimus could be interesting in the treatment of COVID-19.

Mycophenolate mofetil as a potential therapy for MERS and SARS-CoV has also been studied. Although in laboratory studies it seemed to inhibit both MERS-CoV and SARS-CoV, in an animal experiment with marmosets it showed high viral loads with more severe or even fatal disease [45–47].

The role of corticosteroids in SARS-CoV is not conclusive. They were widely used during the SARS-CoV outbreak, but can promote viral rebound and acute respiratory distress syndrome [48]. Importantly, in animal experiments with dexamethasone, it was suggested that in pigs with SARS-CoV infection, dexamethasone could reduce the early pro-inflammatory response, but a prolonged administration could promote viral replication [49]. In a human study that separated SARS-CoV patients into four treatment groups, the best response was seen in the group receiving early high-dose corticosteroids [50].

4.2. Atypical Symptoms in SOT Patients with COVID-19

A remarkable observation is that SOT patients frequently have gastrointestinal symptoms as part of COVID-19. These symptoms have been described in immunocompetent COVID-19 patients, but they appear to be rare (3–5%) [51,52]. Gastrointestinal symptoms from COVID-19 in SOT patients cannot be explained as yet, but may be related to the immunosuppressive treatment, or to the co-medication possibly altering the intestinal microbiome and thus modifying the intestinal reactivity to the viral infection. Again, the number of observations of COVID-19 patients with these manifestations is too small for firm conclusions.

4.3. Secondary Effects of COVID-19 on SOT Patients

In transplantation medicine, COVID-19 has had a noticeable negative influence both on the ambulatory and the hospitalized patients with SOT, with strong psychological effects and increased need for psychological support from transplant physicians, transplant psychiatrists and psychologists, in addition to the somatic effects. This negative influence may become even more obvious as time passes, and the missed follow-up appointments may potentially influence the course of the disease in the coming months. The total impact in this area will only be fully understood in the near future when studies address these issues.

In summary, although further research is urgently needed to give a clearer picture of the impact of SARS-CoV-2 and COVID-19 on the SOT community, the currently available limited data suggest a reduced immediate impact of COVID-19 in respect to severity of disease, most likely due to "protective" immunosuppression. Based on this preliminary observation, we expect a milder disease severity and probably a better outcome in patients with SOT in a population, because they are typically well aware of the risks of viral (and other) infections and thus practice prevention strategies more rigorously, due to knowledge they have acquired prior to the current coronavirus pandemic. In the absence of definitive medical treatment protocols, many treatments have been suggested. Although it is too early for results of large clinical trials, generally in the above-described case reports with COVID-19 stage IIA or IIB, MMF initially is stopped, tacrolimus is reduced, methylprednisolone iv is started, and empiric broad-spectrum antibiotics are given. Hydroxochloroquine or lopinavir-ritonavir/darunavir-cobicistat was given as off-label therapy in some patients. Intravenous gammaglobulins are an alternative treatment for patients at risk of infection-triggered rejection, in whom the immunosuppressive treatment cannot be escalated due to increased drug-related adverse events or fear of increased viral replication.

Whilst more definitive and clinically proven treatments are awaited, the above described treatments can be helpful in the short term and may be reassuring for the SOT community.

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Abbreviations

bilat.	bilateral
CRP	C-reactive protein
CT chest	computed tomography of the chest
ECMO	extracorporal membrane oxygenation
everol	everolimus
GGO	ground-glass opacity
HFOT	high flow oxygen therapy
HCQ	hydroxochloroquine
IS Rx	immunosuppressive therapy
iv	intravenous
IVIG	intravenous immunoglobulin G
MMF	mycophenolate mofetil
MV	mechanical ventilation
NIV	non-invasive ventilation
po	per os
Pred	Prednisone
rh-GCSF	recombinant human granulocyte colony-stimulating factor
Tac	tacrolimus
inh.	inhalation

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