SARS-CoV-2 Infection in Transplant-Related Biology: Where Do We stand?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Since December 2019, the novel coronavirus (SARS-CoV-2) emerged in Wuhan and rapidly spread throughout the world. There are nearly 3 951 905 confirmed cases of novel coronary pneumonia and more than 275 067 deaths worldwide, [JHU data-09/05/2020, *https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd-40299423467b48e9ecf6*]. A great number of patients contracted SARS-Cov-2 pneumonia (COVID-19). SARS-CoV-2 invades human target cells through receptor angiotensin-converting enzyme II (ACE2), which are expressed in the lung, kidney, and ileum and mediate inflammatory responses and immune activities. High plasma levels of proinflammatory cytokines were detected in the infected patients. These factors may predispose transplant patients to high risk of poor outcomes. Therefore, transplant patients might be affected by this coronavirus infection and protection of allografts should receive special attention during this outbreak. In the present study we attempt to delineate the transplant-related biology of SARS-CoV-2 infection.

MeSH Keywords: **Cross Infection • Organ Transplantation • Transplantation**

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Background

Despite improved outcomes in organ transplantation, viral infection is a well-known risk factor for graft dysfunction and even graft loss. Transplant recipients, as an immunocompromised population, are uniquely predisposed to be infected by viruses. Respiratory viruses are the common and potentially serious cause of infection after organ transplantation [1]. Infection with respiratory viruses is a frequent event after organ transplantation, which includes rhinovirus, coronavirus, metapneumovirus, respiratory syncytial virus, influenza A virus, and parainfluenza virus [2]. MERS CoV, SARS, and SARS-CoV-2 are RNA respiratory coronaviruses. It was documented that SARS has a negative impact on liver transplantation [3]. Renal transplant cases with MERS CoV infection tend to have poor allograft outcomes [4]. Respiratory viral infection in the pre- or post-transplant period may be associated with chronic lung allograft dysfunction and acute lung rejection, eventually affecting transplant outcome [5]. However, the novel coronavirus (SARS-CoV-2) is still widely circulating around the word, which poses a huge risk for transplant recipients. There are a number of reasons for the of high risk of SARS-CoV-2 infection in transplant recipients, such as specific allograft factors, immunosuppressive therapies, extensive contact with the healthcare system, and community exposure. Given the potential severity of SARS-CoV-2 in transplant recipients and the large number of cases of SARS-CoV-2, we are suspect that infection has a significant impact on various organ transplantations. Routine medical services are vulnerable during the outbreak of SARS-CoV-2. Therefore, our present review characterizes the transplant-related biology of SARS-CoV-2 infection and summarizes its impact on transplant outcomes.

SARS virus and SARS-CoV-2 virus share a common ancestor. Their similar spike protein 3-D structure with strong binding affinity to human cell receptor is capable of infecting various cell types of multiple organs. Similar to SARS-CoV, SARS-CoV-2 invades human target cells through receptor angiotensin-converting enzyme II (ACE2) [6,7]. Based upon experimental data from single-cell RNA sequencing (scRNA-seq), myocardial cells, type II lung alveolar cells, proximal tubule kidney cells, oesophagus epithelial cells, bladder urothelial cells, and ileum epithelial cells are vulnerable to SARS-CoV-2 infection [7]. High expression of ACE2 not only mediates proinflammatory responses and immune activities, but also participates in cytokine secretion and viral genome replication [8]. High levels of plasma cytokines, including IL-6, IL-1beta, IFN-γ (interferon-γ), IP10 (interferon-inducible-protein 10), and MCP1 (monocyte chemotactic protein-1), were observed in COVID-19 infected patients. Cytokine release syndrome may be associated with disease severity [9]. Therefore, more autopsies are required to unveil the underlying molecular and cellular pathogenesis. Rapid diagnosis of viral infection and dynamic monitoring of various organs' function, including allograft function, are needed to identify which patients are at highest risk, and use of suitable biomarkers might be of significant benefit.

Lung Injury and Transplantation

The lungs are commonly affected by respiratory viruses such as SARS-CoV-2, leading to poor transplant outcomes [10]. Imaging alteration in novel viral pneumonia (COVID-19) is de facto rapid. Chest CT findings showed that patchy/punctate ground-glass opacities appeared in 85.7% of infected patients. Others displayed ground-glass nodules [11]. There appears to be an association between SARS-CoV-2 infection and adverse outcomes of lung transplant patients. This clinical evaluation of this relationship is to be determined. Virus-specific memory CD8+T cells might protect against lethal severe acute respiratory syndrome coronavirus infection [12]. An acute form of lung graft impairment might be triggered by coinfection of COVID-19 and nosocomial bacterial infection [13].Nevertheless, 2 lung transplant recipients infected by SARS-CoV-2 showed asymptomatic or mild infection, indicating no *per se* risk for severe COVID-19 [14].

Kidney Injury and Transplantation

It was surprisingly observed that some patients without respiratory symptoms could develop kidney failure [7]. Due to chronic immunosuppression, kidney transplant recipients are subject to a high risk of contracting COVID-19. Kidney impairment is a common event in COVID-19 patients. It was observed that 52% of cases of acute kidney injury occur among infected kidney transplant recipients [15]. Proteinuria, which is an indicator of renal impairment, was observed in 63% of cases, whereas elevated levels of peripheral creatinine and urea nitrogen were detected in 19% and 27% patients. Importantly, computed tomography (CT) scans showed abnormalities of the kidneys in all infected cases [16]. Nevertheless, a relatively lower rate (0.5%) of acute kidney injury was reported by Guan et al. [17]. Another study reported that 2 patients (1.4%) empirically received kidney replacement therapy [18]. Indeed, it was found that the severe cases were more likely to have kidney injury [17]. Therefore, it is necessary to dynamically monitor renal function and take measures to prevent renal impairment, including continuous renal replacement therapies (CRRT), as early as possible. However, compared with other complications of patients with COVID-19, the prevalence of acute kidney injury (AKI) is lower. The available data indicated that only 0.5% had AKI in 1099 Chinese patients with COVID-19. Three aspects – cytokine damage, systemic effects, and organ crosstalk – may be significant mechanisms of kidney involvement in patients with COVID-19 [19]. These mechanisms have significance in

Table 1. Relevant treatment guidelines for transplant recipients with novel COVID-19 pneumonia.

Classification	Clinical symptom	Laboratory values	Chest imaging	Treatment strategies	Mortality with transplant patients	Reference
Kidney transplantation	less fever as an initial symptom	lower CD8, CD4, and CD3 cell counts	Consistent with viral pneumonia	Reduce the dose of immunosuppressive agents	High early mortality (28% at 3 weeks)	[21]
Liver transplantation	Less fever as the first symptom	Normal or low leucocyte count, Lymphopenia is common,	more extensive lung lesions, and more lower lobes involvement	Maintain normal dose of immunosuppressants		[30]
Heart transplantation	Mild clinical symptoms	Increased IL-6, CRP and proBNP levels	No typical signs of COVID-19	Immunosuppression regimen remain unchanged		[31]
Lung transplantation	Mild clinical symptoms	Lymphocytopenia, increase of c-reactive protein and worsening kidney function	Consistent with viral pneumonia	Reduce immunosuppressive regimen and augment steroids and hold antiproliferative agent	Approximately 20–25%	[13]

guidance of extracorporeal therapy. However, as a chronically immunosuppressed population, renal transplant recipients will face greater risk for critical COVID-19 illness and be different from the general population in the clinical treatment, manifestations, and prognosis of COVID-19 pneumonia [20]. Renal transplantation recipients with COVID-19 have more rapid clinical progression, less fever as an initial symptom, and lower CD8, CD4, and CD3 cell counts [21]. The latest data demonstrates that renal transplant recipients with COID-19 had lower lymphocyte counts and eGFR and higher levels of serum lactate dehydrogenase, IL-6, and procalcitonin. They also have a high early mortality – approximately 28% at 3 weeks. The treatment regimen for these patients mainly consists of reduced immunosuppressant use and other corresponding support treatment. Iranian transplant scientists proposed the detailed diagnosis and treatment for COVID-19 infected kidney transplant recipients [15,22].

Liver Injury and Transplantation

Acute liver injury was reported to be associated with higher mortality among COVID-19-infected patients. Multiple factors may contribute to liver injury, such as drugs, direct cytopathic effects of the virus, sepsis, and uncontrolled immune reaction [23]. It was shown that of 1099 infected cases, 41%, 22.2%, 21.3%, and 10.5% of patients had elevated levels of plasma lactose dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and total bilirubin, respectively [17].

High levels of these enzymes are detrimental to liver allograft function. Antiviral drugs such as Remdesivir are generally metabolized via cytochrome P450 (CYP) 3A enzymes [24]; therefore, administration of antiviral drugs may aggravate hepatic injury. Artificial extracorporeal liver support systems may be utilized to remove not only albumin-bound toxins and small water soluble toxins, but also various cytokines such as IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α) by using super-large-pore membranes [25,26]. This largely prevents the appearance of cytokine release syndrome. An international European prospective study on liver transplant recipients showed that the most common symptoms were fever, fatigue, and myalgia among infected liver transplant recipients. One-third of them had GI symptoms, and 72% were hospitalized. COVID-19 infection was associated with in-hospital and overall fatality rates of 17% and 12%, respectively [27].

Small Bowel Transplantation

Analysis of data on receptor ACE2 expression revealed that ileum epithelial cells are susceptible to SARS-CoV-2 infection [7]. About 3% of cases have diarrhea, which is an uncommon gastroenterologic symptom that should not be overlooked. Viral infection is found in 6.5% of stool specimens [17]. Therefore, attention should be paid to small bowel transplantation, as ACE2 is a key regulator of innate immunity and gut microbial ecology and can cause intestinal inflammation and diarrhea [28].

Several other issues need to be addressed and clarified. It is already known that susceptibility to SARS-CoV-2 is higher in patients undergoing transplantation of various organs (e.g., liver, kidney, heart, lung, intestine/multivisceral). However, the association between post-transplant time, living/deceased donation, post-transplant therapies, and viral infection needs to be further investigated. Although pediatric transplant recipients have a significantly higher risk in respiratory virus infection [29], it remains unclear whether SARS-CoV-2 infection affects the pediatric transplant prognosis and whether this coronavirus can directly attack transplant grafts. The heterologous immunity (i.e., antibodies directed against SARS-CoV-2) may have the capacity to cross-interact with HLA, but this has not been established yet. Although collection of nasopharyngeal specimens is a convenient and patient-acceptable methodology for viral detection, false-negative results may mislead clinicians' judgement. Therefore, bronchoalveolar lavage (BAL) should be performed when clinically indicated.

Conclusions

This transplant population should receive special attention to protect allograft function by providing specific healthcare and protective measures for viral infection. Guidelines for SARS-CoV-2 screening of organ donors need to be developed as SARS-CoV-2 is spreading throughout the world, which is becoming an increasingly significant issue for transplant programs. Transplant clinicians should be on the alert for SARS-CoV-2 to care for immunocompromised recipients. Caution should be taken in use of antiviral drugs or glucocorticoids, which might exert potential negative effects on allografts in practice. We summarized the relevant treatment guidelines for transplant recipients with COVID-19 (see Table 1). Until there is approved vaccination or antiviral prophylaxis, the critical approach of COVID-19 prevention should be isolation of transplant patients.

Conflict of interests

None.

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