

## REVIEW

# Transplantation in the era of the Covid-19 pandemic: How should transplant patients and programs be handled?

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## Summary

Due to the Covid-19 pandemic caused by SARS-CoV-2, transplant programs worldwide have been severely impacted with dwindling numbers of transplantations performed and a complete halt in several areas. In this review we examine whether SARS-CoV-2 infection presents differently in transplant recipients, whom and how we should test, how susceptible the transplant population is to overt infection and describe the range of outcomes. From retrieved published reports on SARS-CoV-2 infections in 389 solid organ transplant recipients reported in the literature, the overall mortality rate was 16.7% ( $n = 65$ ); however for those with mild or moderate Covid-19 disease this was 2.9% and 2.3% respectively; conversely, for those with severe infection the mortality rate was 52.2%. We then address questions regarding halting transplantation programs during this pandemic, whether all human tissues being considered for transplantation are capable of transmitting the infection, and if we should alter immunosuppressive medications during the pandemic.

## KEYWORDS

Covid-19, immunosuppression, kidney transplantation, mortality, outcomes, SARS-CoV-2, solid organ transplantation, waiting list

Transplant programs worldwide have been severely impacted by the Covid-19 pandemic with dwindling numbers of transplantations performed and a complete halt in several areas.

Transplantation, considered largely an elective procedure, has lost its priority. The transplant community now eagerly awaits data often obtained under difficult circumstances during the pandemic and associated with the necessity for hasty reporting. These unusual circumstances have meant that results obtained have been derived from case reports, case series, early registry reports, and short-term small cohorts that have been mostly uncontrolled, not meticulously

designed and, in many instances, there have been conflicting results that have, in some cases, increased confusion.<sup>1-6</sup>

The purpose of this review of the published literature is to try to critically appraise the data and evidence reported from Covid-19 transplant studies in terms of transplant outcomes and transplantation organization, in order to reconcile differences between these reports and recommendations.

## 1 | DOES THE DISEASE PRESENT DIFFERENTLY IN TRANSPLANT RECIPIENTS?

Given the fact that 50–80% of infected patients may be asymptomatic or mildly symptomatic makes comparisons of clinical manifestations between transplant recipients and non-recipients perplexing.<sup>7-9</sup>

There is a relatively low rate of confirmed symptomatic cases among

**List of Abbreviations:** BKV, BK virus; CMV, cytomegalovirus; Covid-19, corona virus disease-19; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; ELITA, European Liver and Intestine Transplantation Association; ELTR, European Liver Transplant Registry; ERA-EDTA, European Renal Association-European Dialysis and Transplantation Association; FDA, Food and Drug Administration; ICU, Intensive Care Unit; MELD, Model End-Stage Liver Disease; MERS, Middle East Respiratory Syndrome; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-corona virus-2.

the transplant population, raising the possibility of higher prevalence of asymptomatic disease in this patient population: a speculation that remains hard to prove.<sup>10-13</sup> This trend reverberates with the less severe forms of infection observed with other coronaviruses in immunocompromised patients.<sup>14</sup> Manifestations of the disease were recently assessed in a systematic review.<sup>15</sup> Based on the figures from various reports and registry data, the frequency of the clinical manifestations in transplant recipients compared to the general population may generally be rounded up as follows<sup>1,16-25</sup>: Amongst symptomatic patients, breathlessness occurs at roughly the same frequency (60–80% of transplant patients and non-transplant patients). Cough and fatigue/myalgia may be more common in transplant recipients: roughly 40% and 20%, respectively, compared to around 4–30% and 10%, respectively, in non-transplant patients. Febrile illness is a major concern that is also difficult to define due to heterogeneous reporting. Roughly 50% of non-hospitalized confirmed cases are febrile and, with a few exceptions, fever occurs in 90–98% of hospitalized non-transplant patients with moderate to severe disease in contrast to only 50–70% of hospitalized transplant patients.<sup>1,16-25</sup> Intriguingly, the most consistent difference in presentation is the higher frequency of gastrointestinal manifestations, particularly diarrhea, around 25–30% in transplant recipients compared to around 3–15% in non-transplant patients.<sup>1,20,21</sup> Lymphopenia affects 30–82% of Covid-19 patients but its value may, hypothetically, be mitigated by the immunosuppressive drugs used.<sup>14,22,26</sup>

## 2 | WHOM AND HOW SHOULD WE TEST?

Unless a screening survey is being performed, there is no clinical justification for universal testing of asymptomatic individuals. For transplant recipients with a fever and respiratory symptoms amidst the pandemic, it would seem reasonable to exclude the infection. The prevalence of respiratory symptoms may be slightly more and fever less among transplant recipients which may justify testing recipients with unexplained respiratory symptoms without fever and vice versa. It is also reasonable to test those with unexplained diarrhea, which is common and sometimes the main presentation in this population.<sup>1,7,20,21</sup>

Testing techniques in transplant recipients remain the same as the general population and are reviewed elsewhere.<sup>27</sup> Briefly, PCR nucleic acid testing is the current gold standard for diagnosis and its results vary based on sample site for example, a bronchoalveolar, sputum, or nasopharyngeal swab are more liable to be positive than oropharyngeal or salivary samples (sensitivities in the general population of 93–100%, 72–89%, 59–94%, and 33–77%, respectively). Repeat testing improves the predictive value and proper sample handling is crucial. On the other hand, serological tests have a potential of having a role in surveillance or epidemiological screening of exposure; but are of limited diagnostic value and their clinical value is yet to be determined. Notwithstanding, at the date of writing this review, most serological tests are still in the process of validation and approval and only a few have received expedited FDA approval that skips the usual

rigorous validation and checking procedures. Whether these tests detect antibodies that are neutralizing or predict infectivity still needs to be proven.<sup>27-30</sup> The main points to consider among transplant recipients are the utility of testing stool samples by PCR when diarrhea is the salient feature<sup>4,16,27</sup> and that the interpretation of antibody testing must be cautious given the anticipated delay in the timeline of seroconversion among immunocompromised patients.<sup>14,27,28,30</sup>

## 3 | HOW SUSCEPTIBLE IS THE TRANSPLANT POPULATION TO OVERT INFECTION AND POOR OUTCOMES?

Answering this question is crucial when making transplant-policy decisions to manage existent patients and assessing prospective transplantation procedures. Current estimates for the general population and particularly for the transplant population are crude and are probably far from the actual true figures.<sup>8,9</sup> Transplant registries have been working to collect this information<sup>1,10-12</sup> and Table 1 summarizes data from many of the published case reports/series.

Results from available reports are in many instances confusing and/or conflicting, probably because they should have been evaluated within a more epidemiologically based framework.<sup>31</sup> Infection rates and fatality rates are difficult to confirm given that systematic screening has not taken place and that many of the current figures include open cases that have neither died nor recovered yet.<sup>8,9</sup> In addition, we need to specify our control groups when defining outcomes in transplant recipients. Ideally, we would want all transplant recipients screened for infection and followed for a reasonable period of time for the rates of infection and outcomes (e.g. hospitalization, mortality, graft dysfunction) compared to both: the general population and waitlisted transplant candidates. Because it is impossible to screen all patients, it would be good to at least have smaller comprehensive registries that record all confirmed cases in a particular area and relate them to a denominator, including all recipients and compare to a control group of all waitlisted subjects in that area.

One set of data that is quite comprehensive comes from the registry of the Italian Society of Nephrology. They screened 25 063 kidney-transplant patients, and confirmed infection in only 218 (0.87%). Of these, 54 died (i.e. 25% of cases, 0.2% of total screened recipients). This may be compared to two groups of controls: a) a cohort of 30 129 dialysis patients constituting 67% of the dialysis population in Italy, of whom 1056 (3.5%) were infected and 409 died (39% of cases, 1.3% of total); and b) a second control group of 201 505 infected cases in the general population with 14% mortality.<sup>11</sup> Despite the shortcomings of registry data, we can draw some reasonable conclusions: the incidence of confirmed cases (and mortality) among kidney recipients is lower than in dialysis patients. French registry data are also enlightening: of 43 311 kidney transplant recipients, 510 (1.2%) had a confirmed infection and 80 (15.7%) died: their median age was 59 years; compared to 94 cases confirmed in 16 835 waitlisted kidney transplant candidates (0.6%) with a median age of 57 years, of whom 69 were dialysis-dependent and 27 died (29%).<sup>32</sup>

**TABLE 1** Summary of the reviewed published reports on Covid-19 in solid organ transplant recipients

| Authors                              | Country     | Number          | Age <sup>a</sup> | Organ                                    | Mortality/<br>mild<br>patients <sup>b</sup> | Mortality/<br>moderate<br>Patients <sup>c</sup> | Mortality/<br>severe<br>patients <sup>d</sup> | Total<br>mortality |
|--------------------------------------|-------------|-----------------|------------------|--|---|---|---|--------------------|
| Gandolfini et al <sup>75</sup>       | Italy       | 2               | 75&52            | Kidney                                   |   | 1/2   |   | 1                  |
| Zhu et al <sup>76</sup>              | China       | 1               | 52               | Kidney                                   |   | 0/1   |   | 0                  |
| Guillen et al <sup>21</sup>          | Spain       | 1               | 50               | Kidney                                   |   |   | 0/1   | 0                  |
| Huang et al <sup>77</sup>            | China       | 1               | 58               | Kidney                                   |   |   | 1/1   | 1                  |
| Banerjee et al <sup>13</sup>         | UK          | 7               | 54               | Kidney                                   | 0/2   | 0/2   | 1/3   | 1                  |
| Wang et al <sup>73</sup>             | China       | 1               | 49               | Kidney                                   |   | 0/1   |   | 0                  |
| Liu et al <sup>78</sup>              | China       | 1               | 50               | Liver                                    |   | 0/1   |   | 0                  |
| Aslam&Mehra <sup>79</sup>            | USA         | 2               | N/A <sup>e</sup> | Heart                                    | 0/1   | 0/1   |   | 0                  |
| Zhang et al <sup>80</sup>            | China       | 5               | 45               | Kidney                                   | 0/5   |   |   | 0                  |
| Aigner et al <sup>81</sup>           | Germany     | 4               |                  | 1 Lung, 1 Kidney, 2 Heart                | 0/3   | 0/1   |   | 0                  |
| Akalin et al <sup>82</sup>           | USA         | 36              | 60               | Kidney                                   | 2/8   | 1/17  | 7/11  | 10                 |
| Hsu et al <sup>83</sup>              | USA         | 1               | 39               | Dual                                     |   | 0/1   |   | 0                  |
| Fernandez Ruiz et al <sup>84</sup>   | Spain       | 18              | 71               | 8 Kidney6 Liver4 Heart                   | 0/6   | 0/4   | 5/8   | 5                  |
| Meziyerh et al <sup>66</sup>         | Netherlands | 1               | 35               | Kidney                                   |   |   | 0/1   | 0                  |
| Kates et al <sup>85</sup>            | USA         | 4               | 60.5             | 1 Kidney, 1 Liver, 1<br>Lung, 1 Heart    | 0/2   | 0/2   |   | 0                  |
| Arpali et al <sup>86</sup>           | Turkey      | 1               | 28               | Kidney                                   |   | 0/1   |   | 0                  |
| Pereira et al <sup>20</sup>          | USA         | 90              | 57               | 46 Kidney17 Lung13<br>Liver9 Heart5 Dual | 0/22  | 0/41  | 16/27 <sup>f</sup>                            | 16                 |
| Zhong et al <sup>87</sup>            | China       | 2               | 37 & 48          | 1 Liver1 Kidney                          |   | 0/2   |   | 0                  |
| Zhu et al <sup>58</sup>              | China       | 10              | 49.5             | Kidney                                   | 0/2   | 0/5   | 1/3   | 1                  |
| Kim et al <sup>88</sup>              | Korea       | 2               | 36 & 56          | Kidney                                   |   | 0/2   |   | 0                  |
| Seminari et al <sup>89</sup>         | Italy       | 1               | 50               | Kidney                                   |   | 0/1   |   | 0                  |
| Li et al <sup>90</sup>               | China       | 2               | 51 & 43          | Heart                                    | 0/1   | 0/1   |   | 0                  |
| Trujillo et al <sup>91</sup>         | Spain       | 26              | 61               | Kidney                                   | <sub>g</sub>                                | <sub>g</sub>                                    | <sub>g</sub>                                  | 3                  |
| Montagud-Marrahi et al <sup>92</sup> | Spain       | 33              | 57.3             | Kidney                                   | 0/7   | 0/13  | 2/13  | 2                  |
| Nair et al <sup>93</sup>             | USA         | 10              | 57               | Kidney                                   | 0/1   | 0/4   | 3/5   | 3                  |
| Alberici et al <sup>94</sup>         | Italy       | 20              | 59               | Kidney                                   | 0/7   | 2/8   | 3/5   | 5                  |
| Mathies et al <sup>95</sup>          | Germany     | 1               | 77               | Heart                                    |   |   | 0/1   | 0                  |
| Mehta et al <sup>96</sup>            | USA         | 35 <sup>h</sup> | 59               | Kidney                                   | 0/1   | 0/29  | 2/5   | 2                  |
| Kolonko et al <sup>97</sup>          | Poland      | 4               | 42               | 3 kidney, 1 liver                        | 0   | 0/3   | 1/1   | 1                  |
| Chen et al <sup>98</sup>             | USA         | 30              | 56               | Kidney                                   |   | 0/23  | 6/7   | 6                  |
| Marcault et al <sup>99</sup>         | France      | 10              | 57               | 9 Kidney,1 heart                         |   |   | 3/10  | 3                  |
| Crespo et al <sup>47</sup>           | Spain       | 16              | 73.6             | Kidney                                   | 0/1   | 0/4   | 8/11  | 8                  |
| Travi et al <sup>46</sup>            | Italy       | 11 <sup>i</sup> | 59               | 7 Kidney,4 Heart2 Dual <sup>i</sup>      | <sub>g</sub>                                | <sub>g</sub>                                    | <sub>g</sub>                                  | 1                  |
| Total Reported                       |             |                 |                  |  | 2/69  | 4/170   | 59/113  | 65/389             |

<sup>a</sup>Age reported as the author's provision of mean or median.

<sup>b</sup>Mortality in non-hospitalized patients.

<sup>c</sup>Mortality in hospitalized ward patients.

<sup>d</sup>Mortality in patients requiring ICU or ventilation.

<sup>e</sup>Not available.

<sup>f</sup>Four patients refused ICU and ventilation.

<sup>g</sup>Severity not clearly specified.

<sup>h</sup>Nine patients in the cohort were excluded from our analysis due to unconfirmed Covid-19.

<sup>i</sup>Two of the 13 cases originally reported in this cohort were judged to have died for reasons unrelated to Covid-19 by the authors and were excluded from our analysis.

A recent initiative by the European Renal Association (ERA-EDTA) collected data from key contact persons in several European countries. The figures are similar to the Italian registry data. For example, in Austria, eight confirmed cases were reported amongst kidney transplant recipients, one of whom died; compared to 44 confirmed cases and 11 deaths in dialysis patients.<sup>10</sup> The rates of infection amongst transplant recipients in Wuhan (China) have been similarly low compared to the general population.<sup>33</sup> The reason these figures are meaningful is that they have both a comprehensible denominator: the number (or estimation) of total population at potential risk; and a control<sup>8,9,31</sup>; non-transplanted patients in the general population or (even more meaningfully) those on the transplant waiting list.

In contrast, data from case series and voluntary registries may give an initial gloomy impression about the fate of transplant recipients in this pandemic, but this can be reconciled with the data mentioned above, if appraised systematically. Voluntary registries<sup>1,34</sup> (that allow physicians to register the cases online) are usually biased<sup>35</sup> towards reporting problematic cases and generally have no clearly defined total population to relate to.

An example of a reported case series comes from Banerjee et al, who reported seven transplant recipients, of whom five needed hospital admission.<sup>13</sup> Of these, four required ICU and one died (14% of total, 25% of ICU admissions). They also reported that their transplant center follows 2082 recipients. This simply translates to a confirmed-case rate of 0.3% of the whole cohort. We also need to note that the "source of those patients" was mostly those requiring hospital admission, and so their mortality rates should be more justly compared to mortality rates among hospitalized and intensive care Covid-19 patients rather than the whole population of Covid-19 patients. The mortality rate for Covid-19 patients in ICUs in the UK is similar: that is, 22%.<sup>36</sup>

Similarly, Pereira et al reported on a group of 90 transplant recipients in New York (46 kidney, 17 lung, 13 liver, 9 heart, and 5 dual-transplant recipients; median age 57 years).<sup>20</sup> Of these, 76% required hospitalization: 27 were classified as severe and had a median age of 67, but only 23 of these entered the ICU. Of the total cohort, 18% died (52% of those admitted to ICU). In order to adequately position these data within a clinical context, we need to know the total number of recipients followed by the center: this was not reported. Thus, this transplant cohort obviously tended to represent patients who required hospitalization. In addition, the mortality rate of 52% of ICU cases should be considered relatively normal if compared to younger control group of non-transplanted patients (mean age 64) admitted into the ICU of another American hospital with an outcome of 50% mortality.<sup>24</sup>

So far, confirmed infection rates among kidney-transplant recipients have been lower than in the general population and, when affected, their outcomes are similar to or even better than their dialysis waitlisted counterparts, so being a transplant patient seems to be safer than being on a waiting list in the Covid-19 era.<sup>1,10,11,33</sup> Transplant candidates on the waiting list, particularly the elderly and those with comorbidities are at high risk of poor outcomes as they fail to

mount a neutralizing immune response to the virus.<sup>37,38</sup> The added survival benefit of transplantation compared to remaining on the waiting-list tips the balance further towards the option of transplantation. This is probably more pertinent in liver-, lung, and cardiac-transplant candidates.<sup>3,14,39-43</sup> For example, data collected by the European Liver and Intestine Transplantation Association (ELITA) and European Liver Transplant Registry (ELTR) showed higher infection rates in waitlisted liver transplant candidates compared to transplanted patients as well as slightly higher mortality rates. Put together this translates into higher absolute mortality figures in non-transplanted candidates.<sup>44</sup> Moreover, without transplantation, the 2 week survival of liver transplant candidates with a MELD score above 30 is less than 50%.<sup>45</sup>

Other factors worth considering when interpreting the data is that not all mortality in recipients with Covid-19 may be attributed to the infection as reported by Travi et al (Table 1)<sup>46</sup> and that the age of the studied cohort is a major determinant of their fate as well as pre-existing comorbidities.<sup>38,47</sup>

#### 4 | SHOULD TRANSPLANTATION BE HALTED DURING THE PANDEMIC?

The number of transplant procedures during the pandemic has fallen by 25–80%.<sup>3,5,6</sup> Deceased donor transplantations has fallen by 90.6% in France and 51.1% in the USA. This was mostly driven by kidney transplantation, but a substantial effect was also seen for heart, lung, and liver transplants, all of which provide meaningful improvement in survival probability.<sup>48</sup>

Transplant programs are challenged by risks of possible transmission to the staff, given the long incubation period of infection during which patients may still be infectious and vice versa. An asymptomatic transplant surgeon who performed kidney transplantation in Italy, became symptomatic and was confirmed with SARS-CoV-2 infection 1 day later.<sup>49</sup> Other issues are the disarray within ICUs and transplant coordination, the risks of exposing recipients to immunosuppression, as well as the paucity of supplies, personnel and intensive-care bed vacancies.<sup>2-6,41</sup>

In contrast, there is the urgency of transplantation as a lifesaving procedure especially among lung and heart candidates, as well as many liver candidates. Chen et al reported accepting a highly suspicious heart graft from a donor with viral pneumonia in the desperate effort to save a child urgently needing a graft to survive.<sup>43</sup> Another team, led by Jing-Yu in China, performed lung transplantation in three recipients with post-Covid-19 lung damage after taking necessary protective procedures.<sup>42</sup> Kidney transplantation, nonetheless, has stood out as a procedure that may be postponed because renal dialysis is available to sustain life.<sup>2</sup> This concept should be refuted for emergency patients, for example, highly sensitized recipients who can receive a suitable graft or those with no access to dialysis.<sup>50</sup> Moreover, given the higher rate of infection and mortality in waitlisted dialysis patients, it may be prudent to hasten, rather than postpone, transplantation in most patients.

The decision on whether to restrict a transplant service or liberalize it must consider patient wellbeing, prevalence of infection within the community, and the capability of a particular center to manage the workload while maintaining infection-control procedures and respecting patient and donor autonomy.

## 5 | PLANNING TO UPSCALE AND RETURN AFTER QUARANTINE?

In order to resume transplantation, it is necessary to maintain infection-control procedures which have been detailed elsewhere.<sup>51-54</sup> Some hospitals have implemented tele-communication media for medical consultations which has mitigated the need for frequent hospital visits.<sup>55</sup> Physicians need to start paying attention to directing their patients to high quality social media platforms for patient education<sup>56</sup>. Logistic issues should also be taken into consideration, such as the availability of staff, venesection for monitoring progress, blood for transfusion, medications, and ICU bed vacancies.<sup>3-6,33,50,51,57</sup>

The next point is the screening of the organ and donor for SARS CoV-2 and subsequent decisions based on the results. Donors and recipients should be screened through an adequate history of exposure, fever, recent hospitalization, or ICU admissions. There is some variation in the test chosen to screen recipients: wholesome perform PCR testing on respiratory samples for all patients, others reserve PCR testing for suspicious cases. With potential donors, most experts are more diligent with lung and intestine grafts, using meticulous clinical exclusion of exposure, chest CT scans (being sensitive in more severe cases) and in most instances PCR testing. It has also been advocated by some to screen and then isolate potential living donors for 3-7 days.<sup>3-5,41</sup>

There is some uncertainty on how to proceed if a recipient or living donor acquired the infection. The American Society of Transplantation suggests at least 4 weeks without symptoms prior to completing the procedure from a recovered donor and the Canadian Society of Transplantation requires two negative swabs, at least 1 day apart, making no comment on infected recipients.<sup>4,51,57</sup> This makes sense given the reports of seroconversion that can occur by 2-3 weeks and the duration of viral shedding in the general population of around 12 days.<sup>4,27,28</sup> Similar recommendations can be applied for quarantining infected transplant recipients, who may shed the virus for longer, an average of 3 weeks (2- >6 weeks).<sup>58-60</sup> Yet not all agree on transplanting a patient with a history of SARS-CoV-2 infection until this is further verified (4).

It is prudent to prioritize lifesaving procedures, as well as low-risk procedures, for example, low immunological-risk recipients who require less immunosuppression and low cardiovascular risk recipients who would probably not need postoperative ICU admission. Desensitization programs requiring elective heavy immunosuppression may be postponed, although transplantation for highly sensitized patients receiving reasonably matched organs should be prioritised. Interestingly a high immunological-risk renal-desensitization procedure was

performed under careful infection-control procedures from a living donor to a patient with no dialysis access in Singapore during the pandemic.<sup>50</sup>

## 6 | ARE ALL HUMAN TISSUES CAPABLE OF TRANSMITTING THE INFECTION?

Whether all human tissues may transmit the virus is debatable.<sup>4,61,62</sup> Extrapolating evidence from previous coronaviruses suggests that transmission should be assumed to be possible from lung and intestinal, and possibly heart tissue, but not necessarily other tissues. To date, there is no traceable report of SARS CoV, MERS or SARS CoV-2 transmission via non-lung organ transplantation.<sup>62</sup> Transmission from blood or other tissues has not been determined, for even though the virus has been recovered from the kidneys, liver, and most body fluids, there is reason to believe that this does not necessarily imply that the tissues are contagious.<sup>62</sup> Indeed there are two reports on patients receiving platelets<sup>63</sup> on one occasion and liver<sup>64</sup> on another occasion from infected donors without becoming infected. Moreover, an absence of clinically evident tissue dysfunction in the donor does not necessarily preclude contamination. The risks of handling deceased infected tissues are not only risk of transmission to the recipient, but also the risk to transplant teams. Infective or not, however, the current notion is that infection should be excluded in potential donors and organs are not accepted if suspicion still exists.<sup>4,40,61</sup>

## 7 | HOW SHOULD IMMUNOSUPPRESSIVE MEDICATIONS BE MANIPULATED DURING THE PANDEMIC?

There is very little evidence to answer this question. SARS CoV-2 infections have been reported in patients receiving all types of anti-rejection therapy, including belatacept and everolimus.<sup>65,66</sup> Clinicians have reacted basically by extrapolating from their practices of managing other viruses, for example, EBV, CMV, and BK viruses. Most would not modulate therapy in mild infections. If the infection becomes more severe, antiproliferative drugs and calcineurin inhibitors are reduced or stopped, whereas steroids are frequently left unchanged or increased in critical cases.<sup>1,2,4,16,20</sup> These empirical actions may be supported by the recently trickling evidence. Positive outcomes reported with dexamethasone in hospitalized non-transplant patients with more than mild Covid-19 may justify the role of steroids.<sup>67</sup> A small cohort suggested better outcomes in transplant recipients converted from tacrolimus to low dose cyclosporine<sup>68</sup> but this needs to be interpreted carefully given the small size of the study and the multiple confounders and co-interventions. Pharmacokinetic interactions between immunosuppression and antimicrobials is another concern.<sup>16,66</sup>

Contrary to these practices, some experimental and (weak) clinical evidence suggests that calcineurin inhibitors (both cyclosporine,<sup>69</sup> and tacrolimus<sup>70</sup>) and mycophenolate<sup>71</sup> may actually have anti-replication

effects on other coronaviruses.<sup>72</sup> There is also the hypothesis that immunosuppression may protect from the viral-induced cytokine storm despite delaying viral clearance.<sup>14,59,72,73</sup> Indeed it was demonstrated that early inflammation and IL-6 levels are mitigated in transplant recipients which may impart favourable outcomes.<sup>60</sup>

Centers should probably avoid pre-emptive changes to their protocols and should rather resume their evidence-based protocols for induction, maintenance, and rejection therapy based on patients' global profiles until more evidence justifies manipulations that could have potential serious consequences on graft and patient survival.<sup>57,60</sup>

Manipulation of immunosuppressive drugs is a very delicate issue. As detailed previously, these drugs may modify the risk of infection, delay viral clearance and change the clinical picture. On the other hand they may have positive effects on the final outcome of the infection and definitely remain the mainstay of preservation of the precious allograft which is crucial for patient well-being and survival.

## 8 | HOW ARE WE FARING AT OUR CENTERS?

Authors of this manuscript work at two centers in France and Egypt. At CHU, Grenoble-Alpes (France), out of almost 1700 kidney-transplant patients, only 7 Covid-19 cases have been recorded with no fatalities. In France, adult kidney-transplant programs were put on hold as of March 15th. Because of the decrease in new Covid-19 cases, our center decided to re-start deceased kidney transplant program as of May 11th; live-kidney transplant program will resume on June 4th. The desensitization program is still on hold. Regarding our immunosuppression protocols we decided not to alter them for the de novo kidney transplant patients for this unusual period. Regarding screening donors for SARS-CoV-2 infection this will be based on 1) the patient's history for the previous 2 weeks, 2) assessing the virus (nasopharyngeal swab) by PCR, and 3) chest CT scan.

At Misr International Hospital, Cairo (Egypt), we perform around 250 living-kidney transplantations per year and have a dedicated desensitization program.<sup>74</sup> With around 1932 kidney recipients in the past 10 years we have had 8 confirmed cases and 1 patient succumbed. Over 50 patients with flu-like symptoms have reported to our center within the past 5 months, and have resolved on an out-patient basis without testing for SARS-CoV-2, which is difficult to obtain for patients with mild symptoms. The program was halted for 2 weeks but then resumed starting with low immune-risk patients who required less intensive induction therapy. New recipients and donors are screened prior to transplantation through appropriate history of symptoms and contact, temperature checks, CRP and chest CT scans. PCR testing is reserved for suspicious cases only. Most stable prevalent transplant out-patients are encouraged to follow via tele-clinics. The flow of tele-clinics is as follows at our centre: laboratory tests are drawn at home; test results are relayed to the physicians; an interactive online video meeting is scheduled and facilitated by the secretariat; patient health records (electronic and/or hard copy) are provided. The tele-clinics have a regular planned schedule with pre-

specified slots and our physicians are free to attend those clinics from their homes or the hospital premises. Patients who are suspected of having Covid-19 are also initially interviewed by an infectious disease specialist online and, when necessary, admitted to isolation areas dedicated for our patients at our center. The transplantation unit is accessed via Covid-19-free corridors, and entry into the transplantation unit is vigilantly surveyed. We have no intention of modifying our immunosuppression protocols pre-emptively, and will restart our desensitization program based on national-infection trends.

## CONFLICT OF INTEREST

The authors have no competing interest.

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