Risks and Benefits of Kidney Transplantation during the COVID Pandemic: Transplant or Not

Transplant?

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ABSTRACT

COVID-19 disease has significantly affected the transplant community by leading to decreased transplant activity and increased waiting list time. As expected, COVID-19 causes substantial mortality in both end-stage renal disease and kidney transplant populations. This is due to underlying chronic kidney disease and a high prevalence of comorbid conditions such as diabetes mellitus, hypertension, and cardiovascular disease in this group. Transplant programs have faced the difficult decision of weighing the risks and benefits of transplantation during the pandemic. On one hand there is a risk of COVID-19 exposure leading to infection while patients are on maximum immunosuppression. Alternatively, there are risks of delaying transplantation, which will increase waitlist-time and may lead to waitlist-associated morbidity and mortality. Cautious and thoughtful selection of both the recipient’s and donor’s post-transplant management is required during the pandemic to mitigate the risk of morbidity and mortality associated with COVID-19. In this review article we aimed to discuss previous publications related to clinical outcomes of COVID-19 disease in kidney transplant recipients, end-stage renal disease patients on dialysis or on the transplant waiting-list and precautions transplant centers should take in decision making for recipient and donor selection and immunosuppressive management during the pandemic. Nevertheless, transplantation in this milieu does seem to be the correct decision with a careful patient and donor selection with safeguard protocols for infection prevention. Each center should do risk assessment based on their patient’s age and medical comorbidities, waitlist time, degree of sensitization, cold ischemia time, status of vaccination, and severity of pandemic in their region.
INTRODUCTION

Kidney transplantation during the emergence of SARS-CoV-2 causing coronavirus disease 2019 (Covid-19) pandemic was wrought with significant challenges worldwide. While this crisis resulted in unbelievable loss in the general community, transplant recipients were particularly susceptible. Transplantation is a resource intensive endeavor and it rapidly became clear that continuation in the face of this pandemic was fraught with unknowns as it pertained to the ability to provide unmitigated clinical care. A survey of 204 centers from 16 countries in May and June 2020 documented that 75% of responding centers held living kidney transplantation (from 67% of North American centers to 91% of European centers). There was a 51.1% drop in transplant activity in USA and 90.6% in France, which was largely driven by reductions in kidney transplantation. Significant decrease in kidney transplant activity during the first peak of the pandemic was due to multiple factors including scarce hospital resources, limited testing capacity, unclear test result sensitivity and reported poor outcomes in kidney transplant recipients with COVID-19.

Expectedly, COVID-19 causes substantial mortality in both dialysis and kidney transplant populations due to their underlying chronic kidney disease and a high prevalence of comorbid conditions such as diabetes mellitus, hypertension, and cardiovascular disease. Transplant programs have faced the difficult decision of weighing the risks and benefits of transplantation during the pandemic. Potent induction agents and higher immunsuppressive doses used early in the post-transplantation period may put patients at risk for developing COVID-19 infection. Contrastingly, the risks of delaying transplantation and increasing wait-time and waitlist-associated morbidity and mortality are not without consideration. Therefore, careful and
thorough selection of the recipients, donors and post-transplant management is required during the pandemic so as not to increase the risk of morbidity and mortality associated with COVID-19. In this review article we aimed to discuss previous publications related to clinical outcomes of COVID-19 disease in kidney transplant recipients, end-stage renal disease (ESRD) patients on dialysis or on the waiting list for transplantation. We will also examine the predictors of poor outcomes in those patients. Lastly, we aimed to discuss what precautions transplant centers should take in decision making for recipient and donor selection and immunosuppressive management during the pandemic.

**PREDICTORS OF MORTALITY IN KIDNEY TRANSPLANT RECIPIENTS WITH COVID-19**

A summary of 10 previous publications reporting mortality rates in kidney transplant recipients with COVID-19 infection are described in Table 1. We included only publications reporting more than 100 patients because risk estimates with small sample sizes are known to suffer from inaccuracy due to random variation. Mortality rates varied between 17.9-32% (mean 22%) in those 2,880 patients. However, most of those patients were hospitalized and thus represent more severely ill patients and may not be generalizable to the broader kidney transplant recipient population. One of the initial largest single center studies from the United States was from our center, Montefiore Medical Center in New York. Overall mortality was 20.5% in 229 kidney transplant recipients and it was higher (37.8%) in patients who required hospitalization. However, 42% of our patients were diagnosed by SARS-CoV-2 IgG antibodies alone without significant clinical symptoms. Kates et al. analyzed the outcomes of 318 kidney transplant recipients from more than 50 transplant centers and reported that 78% of the cohort was hospitalized for COVID19. Among those hospitalized, 20.5% died by 28 days after
diagnosis. Similar in Europe, ERCADO (European Renal Association COVID-19 Database) collaboration database demonstrated a hospitalization rate of 89% and mortality rate of 21.3%.

Kidney transplant recipients from the French Registry of Solid Organ Transplant were compared to a single center cohort of non-transplant patients. 30-day mortality was significantly higher in transplant recipients (17.9% vs 11.4%, respectively, \( p = .038 \)) (19). In a multivariate analysis for predictors of mortality in 10,926 COVID-related deaths in England, solid organ transplantation has the highest hazard ratio of 3.53 and it was 2.5 in those with glomerular filtration rates below 30 mL/min.

Factors associated with higher mortality in kidney transplant recipients were summarized in Table 1. The most common risk factor, reported in almost all the studies, was older age. Poor outcomes in the elderly was also reported in the general population. During the period of March 1 to June 6, 2020, while the overall mortality was 1.39% in 205,639 New York City residents with COVID-19, it was 4.87% for those aged 65–74 years and 14.2% for those aged 75 years and older. Elderly, in general, are usually vulnerable to infection, mainly explained by immunosenescence. This combination of decreased production of naïve T and B cells and dysfunction of innate immune cells coupled with chronic immunosuppressive treatment may worsen outcomes in elderly transplant recipients if they acquire COVID-19. The presence of chronic heart and lung disease, and obesity were also associated with mortality.

**PREDICTORS OF MORTALITY IN ESRD PATIENTS WITH COVID-19**

According to the 2018 USRDS report, 88% of ESRD patients receive in-center hemodialysis treatment. Undergoing this life sustaining treatment in an enclosed facility
together with other patients limits these patients’ ability to self-isolate, which in-turn places them at a higher risk of contracting COVID-19. Compared to the general population, ESRD patients are not only more susceptible to infection, but also have a higher risk of having moderate to severe disease requiring hospitalization thereby leading to increased mortality. We have summarized previous studies reporting mortality rate and its predictors reporting in more than 100 ESRD patients (Table 2)\textsuperscript{9,12,17-29}. The mortality rate was high between 20-32% (mean 25.4%) in a total of 8,370 patients. Hospitalization rates ranged from 57-100% and intensive care unit admission rates were around 10%. ERA-EDTA registry from 7 countries involving 3,285 patients receiving dialysis and 1,013 kidney transplant recipients showed that mortality risk was 1.28 (1.02–1.60) times higher in transplant recipients compared with matched dialysis patients (8). COVID 19 mortality was 44.3% in kidney transplant recipients over 75 years of age compared to 31.4% in dialysis patients. As presented in Table 2, many risk factors have been associated with increased COVID 19 related mortality in ESRD patients, with older age being the most common one. Other predictors of mortality included medical comorbidities like diabetes and heart disease and longer dialysis vintage.

**COMPARING WAITLISTED PATIENTS TO TRANSPLANT RECIPIENTS WITH COVID-19**

Outcomes for patients on the transplant waiting list with COVID-19 infection have not been as widely reported. Studying this patient population is particularly important as the waiting list frequently excludes ESRD patients with significant frailty or severe comorbid conditions. As a result, one would expect this patient population to have better outcomes as compared to all patients on dialysis. Such studies are of interest as they would help make better informed decisions regarding whether to proceed with transplantation during the pandemic.
versus having the patient accrue time on the waiting list. We summarized the studies comparing transplant patients to wait-listed patients with COVID-19 disease in Table 3\textsuperscript{9,11,30-35}.

The incidence of COVID-19 infection was much lower in the transplant recipients than in waitlisted patient, but this could be secondary to testing bias as waitlisted patients could be tested more often. Another explanation is the increased exposure of waitlisted patients to virus while receiving in-center hemodialysis. Most studies, which were done in Europe, identified a much higher COVID-19 related mortality in transplant recipients versus waitlisted patients, ranging 20-37\% vs 5-16\%, respectively \textsuperscript{9,11,31-35}. The largest series came from France for the period March 1st through June 1, 2020 that identified 275 deaths among the 42,812 kidney transplant recipients and 144 deaths among the 16,210 candidates\textsuperscript{35}. This represents an excess of deaths for both populations as compared with the same period the two previous years, which accounted for 44\% and 42\% of the deaths in recipients and candidates, respectively.

While the excess risk of death due to COVID-19 was similar for recipients and candidates in high viral risk area, it was four-fold higher for candidates in the low viral risk area. The authors concluded that transplantation should be suspended in high viral risk areas but maintained outside those areas, both to reduce the excess of deaths of candidates and avoid wasting precious resources. The cumulative incidence rate of COVID-19 among solid organ waitlist candidates in the United Kingdom was 3.8\% through May 20, 2020, with an all-cause mortality rate of 10.2\% among those who developed COVID-19\textsuperscript{11}. In another center in the United Kingdom, waitlisted patients had lower mortality rate (11.3\%) compared to transplant patients (37.1\%) with a HR of 3.36 (95\% CI 1.19-9.50)\textsuperscript{31}. On the other hand, a study in London by Mamode et al. did not identify a mortality difference between both groups (27\% in waitlisted
patients vs 29.8% in transplant recipients) (23). In contrast, Craig-Shapiro et al in New York detected a much higher mortality in 56 waitlisted patients at 34% vs 16.3% in 80 renal transplant recipients (21). In USA, kidney waiting list mortality was higher after the national emergency declaration on March 13, 2020 (adjusted hazard ratio [aHR], 1.37; 95% CI, 1.23–1.52). The hazard of waitlist mortality was not significantly different for liver, pancreas, lung, and heart. Mortality risk was highest in New York City donation service area (aHR 2.52) and in blacks (aHR 1.41) compared to whites.

Differences in waitlist eligibility among transplant centers may explain the different outcomes. Some centers may accept higher risk candidates with higher number of comorbidities, which would increase the risk of mortality in their waitlisted patients. More studies comparing outcomes between these two groups are needed at this time to better inform patients of their risk of proceeding with transplant versus waiting on the list during the pandemic. Massie et. al. built a simulation model of waitlist and post-transplant mortality in the context of COVID-19, which showed that transplantation provided survival benefit in modeled scenarios, except when the case fatality rate of COVID-19 in transplant recipients greatly exceeded that of waitlisted patients.

DONOR ASSESSMENT DURING PANDEMICS

American Society of Transplant Surgery (ASTS) COVID-19 Strike Force Guidance was tailored to aggressively test all donors and recipients regardless of symptomatology. To date there have been innumerable protocols to assess donors for coronavirus that include donor history, reverse transcriptase polymerase chain reaction (RT-PCR), presence of lymphopenia and/or axial chest imaging. Given ongoing wide-spread community transmission, viral testing of
at least one sample from the respiratory tract by RT-PCR for SARS-CoV-2 should be performed within 3 days of procurement (Table 4). A second viral test should be performed 24-hours after the initial test and within 24-48 hours of procurement when feasible. Chest CT findings of ground glass opacities should be assessed in the context of COVID-19 disease due to 10-20% chance of false negative RT-PCR result. Although, the risk of SARS-CoV-2 transmission through deceased donor, non-pulmonary, organs is very low\textsuperscript{39}, individuals with active RT-PCR positivity for SARS-CoV-2 should not be accepted as kidney donors. For donors previously known to have had COVID-19, it is suggested that the initial COVID infection occurred between 21 and 90 days prior to donor evaluation, irrespective of repeat NAT test results, and at least 30 days should have passed after symptom resolution.

All living donors should have viral testing of at least one sample from the respiratory tract by RT-PCR for SARS-CoV-2 within 3 days of donation. For living donors who were previously known to have had COVID-19, at least 30 days should have passed after all symptoms were resolved and should have negative chest X-ray. Living donors ideally should be vaccinated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before transplantation.

During the pandemic, uneasiness about surging coronavirus rates in the hemodialysis centers ushered in a desire to avoid delayed graft function (DGF) if possible. Post-transplant oliguria would relegate the patient toward an extended in-house hospital stay to avoid coronavirus exposure in a dialysis unit. As such, donor characteristics tended to favor younger ages and lower kidney donor profile index. Moreover, consideration was given toward ensuring lower cold ischemia times to minimize DGF. This proved to be particularly challenging as
aviation disruption lead to severe logistic challenges for moving organs across the country. Lastly, donor after cardiac death donors were less favored due to their propensity for DGF.

RECIPIENT ASSESSMENT FOR TRANSPLANTATION DURING PANDEMICS

As discussed above, older age has been shown to be the best predictor of mortality in multivariate analysis. Patients over age of 65, especially if they have additional comorbidities such as cardiovascular disease and diabetes mellitus, transplantation were deferred at the peak of the pandemic (Table 4). Another at risk group is comprised of highly sensitized patients with donor-specific antibodies who have an increased risk for development of acute rejection that might require augmented immunosuppressive medications, such as anti-thymocyte globulin and/or rituximab. Though there is scant evidence to assign coronavirus progressive risk to anti-thymocyte globulin, a practice of avoidance when possible has been adopted. However, highly sensitized patients with cPRA over 95% receiving an offer from a donor without any donor-specific antibody and/or miss-match could be considered for transplantation. Another important factor in decision making is patient’s waiting time on the list. While the patients on top of the waiting list can afford to wait until the pandemic resolves, patients with an expected waiting time of more than 3 years on the list can be considered for transplantation if they do not have significant co-morbidities. Waiting time is shorter in simultaneous kidney and pancreas transplantation and those patients require potent induction agents that it would be advisable to defer transplant at the peak of pandemics. For simultaneous kidney and heart or liver transplantation, allocation is driven by heart and liver transplantation and sickest patients receive the offer and transplant should not be deferred during pandemics while the survival without transplantation is limited in those patients.
Perhaps the area most rife for debate is when to transplant patients after they have been infected or vaccinated. The ASTS Strike Force most recent recommendation is to proceed with transplant once the patient is without evidence of active infection and has two consecutive negative PCR test one week apart prior to transplantation. More importantly, the patient should wait at-least 30 days after resolution of COVID-associated symptoms before consideration for transplantation\textsuperscript{38}. These patients should have an updated cardiac and pulmonary assessment before they are considered for transplantation due to effects of COVID-19 disease on heart and lung function. Patients that have received the first dose of coronavirus vaccine (Moderna and Pfizer BioNtech) and are awaiting the second dose can be transplanted, though there is mounting evidence that these patients do not develop an appropriate response. Initial reports documented a lower antibody response (6.2%-17%) to vaccination after first dose of mRNA vaccination\textsuperscript{40-42}, which is in contrast with the robust early immunogenicity observed in the general population following mRNA vaccination\textsuperscript{43-45}. However, antibody response rate was higher in a small group of ESRD patients\textsuperscript{41}.

Patients ideally should be vaccinated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before transplantation. Uncertainty sometimes arises if patients are in between their first and second vaccine dose and they receive an excellent kidney transplant offer. In this scenario, we allow the patients to make the decision on whether to pursue with transplantation or not but recommend forgoing the second dose of the vaccine should they opt to accept the organ offer. Revaccination should start 3 months after transplantation. Nevertheless, transplant center should educate fresh transplant recipients to take all
precautionary measures to reduce the chance of getting infected: limiting visitors, 6 feet distance, wearing masks, and consider home based blood draw if feasible.

IMMUNOSUPPRESSION MANAGEMENT DURING COVID-19 PANDEMIC

After infection detection, lowering immunosuppressive regimen may help recover specific immunity, which may help controlling viral replication. Theoretically, this may lead to lesser disease severity, especially given the documented lymphopenia and low T-cell counts in these recipients. However, during the late phases of the disease, which is mainly considered a state of immune dysfunction, withdrawal or significant reduction of immunosuppressive drugs could hypothetically exacerbate this dysfunctional immune response. Bae et al included 69,884 recipients (64,849 transplanted in the pre-pandemic period and 5,035 in the pandemic era) and reported a decrease in the use of lymphocyte-depleting induction agents from 73.2% in the pre-pandemic era to 67.8% in the pandemic era. The use of lymphocyte-depleting agents was associated with decreased acute rejection rates but was not associated with increased mortality. Two national registries in France reported that renal transplant recipients who died from COVID-19 were more frequently within their first year of transplantation, but there was no association between anti-thymocyte globulin or alemtuzumab use and death. A single center in New York reported a safe use of anti-thymocyte globulin at the peak of the pandemic.

Given that T-cell function and proliferation is the mainstay of the immune response against generalized viral infections, withdrawal or reduction of antimetabolites such as mycophenolate mofetil of azathioprine was a practical approach in mild cases not requiring hospital admission (Table 5). A review by Marinaki et al. including 63 articles with 420 patients
found reduction or discontinuation of immunosuppression in 58% of the patients, with antimetabolite discontinued in 91% of patients and CNI in 58%\textsuperscript{10}. Calcineurin inhibitor reduction or withdrawal was most frequently done in more moderate to severe disease, particularly in patients in the intensive care unit. Steroids, on the other hand, were frequently left unchanged or increased in some cases. The RECOVERY trial demonstrated mortality benefit in treatment with dexamethasone 6 mg daily for patients with COVID-19 requiring oxygen. The World Health Organization consequently recommended the use of systemic corticosteroids in severe and critical cases as the standard of care\textsuperscript{48}.

Neutralizing monoclonal antibody treatment has been used successfully in mild cases not requiring hospital admission. In a randomized phase 2 trial of a single intravenous infusion of neutralizing antibody LY-CoV555 decreased the COVID-19 related hospitalization or emergency room visit (1.6%) compared to placebo group (6.3\%)\textsuperscript{49}. Another randomized double-blind study using a combined cocktail (REGN-COV2) decreased the medical visit from 6% to 3\%\textsuperscript{50}.

Interleukin-6 (IL-6) has been shown to be the driving cytokine in severe cases and high IL-6 levels were shown to be associated with mortality. Early observational cohort studies of tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, found that patients receiving tocilizumab had reduced mortality compared to standard of care\textsuperscript{51,52}. However, two randomized, double-blind, placebo-controlled, multicenter trials did not show any benefit with tocilizumab therapy\textsuperscript{53,54}. In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival\textsuperscript{55}.
multicenter cohort study of 80 hospitalized kidney transplant recipients in Spain, tocilizumab treatment did not have an impact on outcome\textsuperscript{56}.

In a multicenter, randomized, placebo-controlled trial, patients receiving a 10-day course of remdesivir, an inhibitor of viral RNA polymerase, had a shorter time to recovery compared to placebo (11 vs 15 days, ratio for recovery 1.32, 95% CI 1.12-1.55), with the most significant improvement seen in non-intubated patients receiving supplemental oxygen but no mortality benefit was observed\textsuperscript{57}. Baricitinib, a Janus kinase inhibitor, plus remdesivir did not decrease mortality but patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control\textsuperscript{58}.

Passive antibody therapy through the use of convalescent plasma is another potential therapy for COVID-19, which may be effective through viral neutralization\textsuperscript{59}. A randomized trial from China revealed a trend towards clinical improvement with plasma therapy (51.9\% vs 43.1\%) but failed to meet statistical significance (p=0.26)\textsuperscript{60}. A meta-analysis of 10 studies reported that treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes\textsuperscript{61}. Plasma exchange has been used to remove the circulating cytokines in small case series\textsuperscript{62,63} but also has the potential to remove antibodies to SARS-CoV-2 and could be combined with convalescent plasma.

**CONCLUSION**

We have reviewed the published data to answer the question of whether to “transplant or not transplant” during pandemic. The current available data does not particularly support
one choice over the other. However, the higher incidence of disease observed in the waitlisted population (likely due to increased exposure during dialysis) suggests that proceeding with transplant with protocols that safeguard against infection combined with careful patient and donor selection seems most appropriate at this time. Still, each center should do risk assessment based on their patient’s age and other medical comorbidities, waiting time on the list, degree of sensitization, cold ischemia time, status of vaccination, and severity of the pandemic at their region.

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| Study                        | Total number of patients | Overall Mortality | Predictors of Mortality                                                                 |
|------------------------------|--------------------------|-------------------|----------------------------------------------------------------------------------------|
| Ravanan et al.\(^{11}\)     | 489                      | 26%               | n/a                                                                                     |
| Marinaki et al.\(^{10}\)    | 420                      | 22%               | n/a                                                                                     |
| Kates et al.\(^{13}\)       | 318                      | 17.9%             | Older age, congestive heart failure, obesity, chronic lung disease, pneumonia on imaging, and lymphopenia(<0.5 thousand/ml) |
| Caillard et al.\(^{6}\)     | 306                      | 17.9%             | Age over 60 years, cardiovascular disease, dyspnea, fever, and creatinine level > 115 \(\mu\)mol/L |
| Hillbrand et al.\(^{9}\)    | 305                      | 21.3%             | Older age                                                                              |
| Sanchez-Alvarez et al.\(^{12}\) | 286                    | 18.6%             | Older age, pneumonia on imaging                                                        |
| Caillard et al.\(^{5}\)     | 279                      | 22.8%             | Age over 60 years, cardiovascular disease, dyspnea                                       |
| Azzi et al.\(^{4}\)         | 229                      | 20.5%             | Older age, deceased donor transplant recipients, lack of receipt of influenza vaccination previous year |
| Cravedi et al.\(^{7}\)      | 144                      | 32%               | Older age, respiratory rate >20 per min, low estimated glomerular filtration rate, and elevated serum interleukin-6 levels |
| Fava et al.\(^{8}\)         | 104                      | 27%               | Older age, acute respiratory distress syndrome, elevated lactic dehydrogenase levels on admission |
### TABLE 2. Mortality and predictors of mortality in end-stage renal disease patients with COVID-19

| Study                  | Total Number of Patients | Overall mortality | Predictors of Mortality                                                                 |
|------------------------|-------------------------|-------------------|----------------------------------------------------------------------------------------|
| Jager et al.\(^{20}\)  | 3285                    | 21.2%             | Older age, male gender                                                                 |
| Quintaliani et al.\(^{25}\) | 1368                  | 32.8%             | n/a                                                                                     |
| Hillbrands et al.\(^9\) | 768                     | 25%               | Frailty score, older age, obesity, dyspnea, high body temperature, high heart rate and elevated liver enzymes at presentation |
| Sanchez-Alvarez et al.\(^{12}\) | 582                    | 25%               | Age, pneumonia on imaging                                                               |
| Ng et al.\(^{24}\)    | 419                     | 32%               | Older age, mechanical ventilation, vasoactive medication use, lymphopenia, elevated blood urea nitrogen and ferritin |
| Sosa et al.\(^{27}\)  | 325                     | 27.7%             | n/a                                                                                     |
| Weiss et al.\(^{28}\) | 306                     | 27.8%             | Age over 65 years, longer dialysis vintage                                              |
| Corbett et al.\(^{17}\) | 300                    | 20%               | Older age, inactive on kidney transplant waitlist                                        |
| De Meester et al.\(^{18}\) | 234                    | 29.6%             | Male gender, diabetic nephropathy as cause of renal disease and diabetes mellitus       |
| Xiong et al.\(^{29}\) | 154                     | 30.8%             | Older age, elevated D-dimer                                                            |
| Sim et al.\(^{26}\)   | 133                     | 22.6%             | Older age, ischemic heart disease, heart failure, diabetes mellitus                     |
| Manganaro et al.\(^{23}\) | 130                    | 24.6%             | Male sex, cardiovascular disease                                                       |
| Reference          | Sample Size | Prevalence | Findings                                                                 |
|--------------------|-------------|------------|--------------------------------------------------------------------------|
| Lano et al. \(^{22}\) | 129         | 28\%       | Need for oxygen therapy at presentation, lymphopenia                      |
| Keller et al. \(^{21}\) | 123         | 24         | Fever, C-Reactive Protein on admission                                    |
| Fisher et al. \(^{19}\) | 114         | 28         | Elevated respiratory rate and lower oxygen saturation on admission, initial elevated procalcitonin, ferritin, lactic dehydrogenase levels and lower lymphocytes count |
| Study                  | Total number of wait-listed COVID-19+ Patients | Incidence of COVID-19 in wait-listed patients | Overall mortality in wait-listed patients | Total Number of COVID-19+ transplant recipients | Incidence of COVID-19 in transplant recipients | Overall Mortality in transplant recipients |
|------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------|-------------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Thaunat et al. 35      | 478                                           | 2.95%                                         | 12.6%                                     | 606                                             | 1.4%                                          | 20%                                         |
| Ravanan et al. 11      | 197                                           | 3.8%                                         | 10.2%                                     | 470                                             | 1.4%                                          | 26.4%                                       |
| Hillbrands et al. 9    | 148                                           | n/a                                          | 5.4%                                      | 23                                              | n/a                                           | 30%                                         |
| Craig-Shapiro et al. 32| 56                                            | n/a                                          | 34%                                       | 80                                              | n/a                                           | 16.3%                                       |
| Clarke et al. 31       | 53                                            | 17.7%                                        | 11.3%                                     | 16                                              | 6.8%                                          | 37.5%                                       |
| Mamode et al. 33       | 52                                            | 4.2%                                         | 27%                                       | 121                                             | n/a                                           | 29.8%                                       |
| Mohamed et al. 34      | 32                                            | 9.97%                                        | 15.6%                                     | 28                                              | 1.9%                                          | 32%                                         |
TABLE 4. Clinical approach to living and deceased donor sand recipients during COVID-19 Pandemic

DONOR ASSESSMENT

1. Deceased and living-donor transplant activity should be assessed at each center based on COVID-19 pandemic severity at their region.
2. One sample from the respiratory tract by RT-PCR for SARS-CoV-2 should be performed within 3 days of procurement. A second viral test be performed 24-hours after the initial test and within 24-48 hours of procurement when feasible.
3. For donors previously known to have had COVID-19, it is suggested that the initial COVID infection occurred between 21 and 90 days prior to donor evaluation, irrespective of repeat NAT test results, and at least 30 days passed after symptom resolution.
4. Chest computerized tomography should be negative for COVID-19 suspicious pneumonia.
5. Consideration should be given toward ensuring lower cold ischemia times to minimize delayed graft function.
6. For living donors who were previously known to have had COVID-19, at least 30 days should have passed after all symptoms were resolved.
7. Living donors should be vaccinated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before transplantation.

RECIPIENT ASSESSMENT

1. Patients over age of 65, especially if they have additional comorbidities such as cardiovascular disease and diabetes mellitus, transplantation could be deferred at the peak of pandemics.
2. Transplantation in highly sensitized patients with use of anti-thymocyte globulin and/or rituximab should be assessed case by case considering recipients age and other co-morbidities, degree of HLA-matching and miss-matching, and severity of the pandemic at the region.
3. For recipients who were previously known to have had COVID-19, at least 30 days should have passed after all symptoms were resolved and should have an updated cardiac and pulmonary assessment before they are considered for transplantation.
4. Patients ideally should be vaccinated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before transplantation.
**TABLE 5: Management of kidney transplant recipients with COVID-19**

**Mild cases not requiring hospital admission**
1. Continuation of current immunosuppression with calcineurin inhibitor and prednisone.
2. Decrease in antimetabolite dose (25-100%)
3. Monoclonal neutralizing antibody treatment (LY-CoV555 or REGN-COV2)

**Moderate cases requiring hospital admission**
1. Continuation of current immunosuppression with calcineurin inhibitor treatment with 25-50% dose reduction
2. Dexamethasone 6 mg daily for 5-10 days
3. Hold antimetabolite

**Severe cases requiring intensive care unit admission**
1. Holding calcineurin inhibitor and anti-metabolite
2. Dexamethasone 6 mg daily for 5-10 days