<u>Kidney involvement with covid -19, in</u> <u>recipients of renal transplantation</u>

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- Etiology of AKI in covid-19 disease
- Presentation of covid -19 virus in kidney transplant patients
- Summary and recommendation

Prevalence of AKI in covid-19 disease and kidney transplant patient

• The impact of COVID-19 on patients with pre-existing kidney impairment, including those with chronic kidney disease, kidney transplant recipients, and individuals on hemodialysis (HD) has not yet been clearly established.



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Table 1.	Baseline characteristics of the study population according to the presence of COVID-19 disease after kidney
ransplan	ation

Demographic Characteristics	All Patients, n=1216	COVID-19–Positive Patients, n=66	COVID-19–Negative Patients, n=1150	P Value ^a
Age, yr	54.1±13.4	56.4±12.5	54.0±13.4	0.14
Men, no. (%)	777 (64)	37 (56)	740 (64)	0.17
Non-White, no. (%)	222 (24)	24 (36)	198 (17)	< 0.001
Blood group, no. (%)				0.90
Α	463 (38)	23 (35)	440 (38)	
В	194 (16)	12 (18)	182 (16)	
0	489 (40)	28 (42)	461 (40)	
AB	70 (6)	3 (5)	67 (6)	
Cause of ESKD, no. (%)				0.13
Glomerulopathies	254/1206 (21)	7/66 (11)	247/1140 (22)	
Diabetes	195/1206 (16)	12/66 (18)	183/1140 (16)	
Vascular	209/1206 (17)	16/66 (24)	196/1140 (17)	
Other	548/1206 (46)	31/66 (47)	514/1140 (45)	
Deceased donor, no. (%)	1053 (87)	64 (97)	989 (86)	< 0.001
Prior kidney transplant, no. (%)	132 (11)	8 (12)	124 (11)	0.69
Time on dialysis prior to transplantation, mo ^b	49.4±42	57.8±46.2	48.8±41.8	0.09
Multiorgan recipients, no. (%)	96 (8)	4 (6)	Age (8)	0.57

Plus-minus values are means ± SD.

"P values are for the comparisons between COVID-19-positive and COVID-19-negative patients.

^bTime on dialysis prior to transplantation was available in 1078 patients.

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Clinical Easturas and Outcomes	All Patients,	Invasive Mechanical	No Invasive Mechanical
Cambai reatures and Outcomes	n=66	Ventilation, n=15	Ventilation, n=51
Features at diagnosis			
Clinical presentation, no. (%)			
Fever	51 (77)	12 (80)	39 (76)
Cough	38 (58)	11 (73)	27 (53)
Dyspnea (exertional or rest)	26 (39)	12 (80)	14 (27)
Diamhea	17 (26)	2 (13)	15 (29)
Anosmia/ageusia	7 (11)	O (O)	7 (14)
Laboratory tests*			
white blood cell count, 1000/ها, median (range)*	5.9 (1.6-14.2)	7.4 (2.6-14.2)	5.3 (1.6-13.2)
Absolute lymphocyte count, /µl	528 (80-1300)	473 (80-1180)	548 (169-1300)
C-reactive protein, mg/L	115 (0-335)	159 (18-316)	96 (0-335)
Chest x-ray/pulmonary CT scan, ^a no. (%)			
Multifocal/bilateral patchy opacities	38/56 (68)	12/13 (92)	26/43 (60)
Lobar opacities	3/56 (5)	1/13 (8)	2/43 (5)
No acute findings	15/56 (27)	0/13 (0)	15/43 (35)
Immunosuppressive treatment, no. (%)			
MMF/MPA/AZA	61 (92)	13 (87)	48 (94)
CNI	57 (86)	14 (93)	43 (84)
Belatacept	6 (9)	1(7)	5 (10)
Steroids	55 (83)	13 (87)	42 (82)
Treatment and outcome			
Change in immunosuppression, no. (%)			
Discontinued only MMF/MPA/AZA	38/61 (62)	13 (100)	25/48 (52)
Discontinued only CNI	2/57 (4)	2/14 (14)	0
Belatacept infusion postpone	1/6 (17)	0	1/5 (20)
No change	24 (36)	2 (13)	22 (43)
Discontinued all immunosuppression	1 (2)	1 (7)	0
Anti-COVID-19 therapies, no. (%)			
Hydroxychloroquine	7 (11)	4 (27)	3 (6)
Tocilizumab	1 (2)	O (IO)	1 (2)
Eculizumab	2 (3)	O (O)	2 (4)
Outcomes, no. (%)			
AKI	28 (42)	13 (87)	15 (29)
RRT required	7 (11)	7 (47)	0 (0)
Died	16 (24)	11 (73)	5 (10)
Recovery	50 (76)	4 (27)	46 (90)

Table 2. Clinical features and outcomes of kidney transplant recipients with COVID-19

Data are displayed as n (%) or median (range). CT, computed tomography; MMF, mycophenolate moletil; MPA, mycophenolic acid; AZA, azathioprine; CNI, calcineurin inhibitor.

12/4/2020[®]Data recorded in the 60 hospitalized patients, with missing data for two patients in the invasive mechanical ventilation group and two patients in the noninvasive mechanical ventilation group, for patients admitted to other hospitals.

Significance Statement

Although studies have found coronavirus disease 2019 (COVID-19) to be associated with high morbidity and mortality among kidney transplant recipients, risk factors for COVID-19 among kidney transplant patients remain poorly defined. In this prospective cohort study in France, the authors enrolled 1216 kidney transplant patients, 66 (5%) of whom were diagnosed with COVID-19. The mortality rate associated with COVID-19. for the overall study population was 1% and 24% among COVID-19positive patients. Factors that were independently associated with COVID-19 included non-White race and comorbidities, including obesity, diabetes, and asthma and chronic pulmonary disease. In the context of COVID-19, it is imperative that policy makers integrate information about risk factors to help clinicians balance benefits and risks and better advise patients about potential risks.

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The impact of COVID-19 on kidney transplantation

Sami Alasfar & Robin K. Avery 🖂

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COVID-19 and nephrology



Donor testing

- the American Society of Transplantation (AST) recommended epidemiological, clinical and laboratory assessment of potential deceased donors
- Epidemiological assessment includes identification of factors such as residence in or travel to high incidence areas and recent exposure to individuals with COVID-19. Clinical assessment includes assessment of COVID-19 symptoms
- laboratory assessment comprises nucleic acid testing of at least one sample from the upper or lower respiratory tract for SARS-CoV-2 within 3 days of organ procurement
- Donors with recent COVID-19 might be considered for donation if they had repeated negative nucleic acid testing at least 24 h apart and resolution of symptoms more than 28 days before organ procurement⁵



• Overall mortality was 20.5% but significantly higher (37.8%) in the patients who required hospitalization.

- Twenty-three percent of the hospitalized patients required kidney replacement therapy and 6.3% lost their allografts
- In multivariable analysis, older age, receipt of deceased-donor transplantation, lack of influenza vaccination in the previous year and higher serum interleukine-6 levels were associated with mortality.



- Of the 1073 patients enrolled, 305 (28%) were kidney transplant and 768 (72%) dialysis patients with a mean age of 60 ± 13 and 67 ± 14 years, respectively
- Mortality was 21.3% in kidney transplant and 25.0% in dialysis patients.
- Mortality was primarily associated with advanced age in kidney transplant patients
- in the first year after kidney transplantation, patients may be at increased risk of COVID-19-related mortality as compared with dialysis patients on the waiting list for transplantation.

CORRESPONDENCE

Covid-19 and Kidney Transplantation

186 Citing Articles

TO THE EDITOR:

Kidney-transplant recipients appear to be at particularly high risk for

June 18, 2020 N Engl J Med 2020; 382:2475-2477 DOI: 10.1056/NEJMc2011117 Metrics Chinese Translation 中文翻译 CORRESPONDENCE

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- A total of 26 recipients (72%) were male, and the median age was 60 years (range, 32 to 77). Fourteen recipients (39%) were black, and 15 recipients (42%) were Hispanic. Twenty-seven recipients (75%) had received a deceased-donor kidney; 34 recipients (94%) had hypertension, 25 (69%) had diabetes mellitus, 13 (36%) had a history of smoking tobacco or were current smokers, and 6 (17%) had heart disease.
- Thirty-five of the patients (97%) were receiving tacrolimus, 34 (94%) were receiving prednisone, and 31 (86%) were receiving mycophenolate mofetil or mycophenolic acid.

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- The most common initial symptom was fever (in 21 patients [58%]), and diarrhea was observed in 8 patients (22%).
- At a median follow-up of 21 days (range, 14 to 28), 10 of the 36 kidney-transplant recipients (28%) and 7 of the 11 patients who were intubated (64%) had died.
- Two of the 8 patients who were monitored as outpatients died at home; both were recent kidney-transplant recipients who had received antithymocyte globulin within the previous 5 weeks

• Etiology of AKI in covid-19 disease

Complement Activation in COVID-19

- The complement system is an important component of innate immunity that is essential to respond rapidly to infection.
- During inflammation, both acute and chronic, activation of the complement system promotes the elimination of pathogens.
- Dysregulation of the complement system may lead to acute lung disease after a highly pathogenic viruses infections

Hypercoagulability and Thrombosis in COVID-19

- In general, altered hemostasis due to viral infections often leads to vascular complications like thrombosis and or hemorrhage.
- Vascular and endothelial changes by the virus as well as inherited host factors help define the clinical presentation
- Hypoxia associated with COVID-19 pneumonia increases blood viscosity both directly and through hypoxia-inducible transcription factor-dependent signaling pathway thereby promoting thrombosis

The Mechanisms of SARS-CoV-2 Associated Kidney Injury

- The exact mechanism of kidney involvement is unclear and likely multifactorial.
- Kidney disease may be caused by SARS-CoV-2 binding to the ACE2 receptor on kidney cells that allows the virus to enter
- Moreover, normal kidney and intestinal tract have higher ACE2 expression than lung tissue
- Detection of coronavirus in the kidneys and urine of patients with SARS-CoV and SARS-CoV-2 supports the theory that the virus can directly damage the kidneys
- Preliminary evidence in postmortem examinations of kidney tissue from six patients found severe acute tubular necrosis and lymphocyte infiltration.







The Mechanisms of SARS-CoV-2 Associated Kidney Injury

- Moreover, in one autopsy of a kidney transplant patient who died of COVID-19, viral inclusion structures were found in the endothelial cells of the kidney
- Viral infection could induce tubular damage through the deposition of the MAC complex (the final step of the complement cascade) on tubules and infiltration of CD68⁺ macrophages in the tubule- interstitium
- Puelles et al. showed the presence of SARS-CoV-2 RNA and proteins in all kidney areas, especially in glomerular cells in autopsies of three of six COVID-19 patients.
- Kidney biopsies in two Afro-American patients with high-risk APOL1 genotype and COVID-19 infection showed a collapsing focal segmental glomerulosclerosis

The Mechanisms of SARS-CoV-2 Associated Kidney Injury

 Other indirect mechanisms that potentially lead to tubular injury are sepsis, cytokine storm syndrome, shock/hemodynamic instability, rhabdomyolysis, and hypoxia of kidney tissue

• Chronic immunosuppression is a well-known risk factor for viral and bacterial infections, but it is also crucial to prevent graft rejection.

- The transplant community is puzzled in trying to understand the best therapeutic approach, in the absence of any strong clinical data
- So far, initial presentation in transplant recipients has been reported heterogeneous to other hosts and many patients did not report contact with infected individuals
- Common symptoms at disease onset have been fever, cough, asthenia, myalgias, and diarrhea

Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. . Covid-19 and kidney transplantation. N Engl J Med. (2020) 382:2475–7. 10.1056/NEJMc2011117 [<u>PMC free article</u>] [<u>PubMed</u>] [<u>CrossRef</u>] [<u>Google Scholar</u>]

• In a study of 36 transplant recipients, however, fever was less common than in general COVID-19 patients

In multiple series, transplant patients show numerous radiopacity and patchy shadows on chest radiographs often at presentation

Laboratory exams often showed lymphopenia with lower CD3, CD4, and CD8 T cells especially in those patients who had received antithymocyte globulin in the weeks before the infection

- According to the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) guidelines ,in patients with COVID-19 and without pneumonia, complete withdrawal of immunosuppressants -particularly calcineurin inhibitors (CNI)- is discouraged
- Reduction of the dosage of CNI, and withdrawal of mycophenolate, azathioprine, or mTOR-inhibitors should be individualized considering the severity of the disease

- The concurrent use of antivirals and anti-inflammatories should be carefully considered with attention to drug-drug interactions that may affect the half-life of immunosuppressant drugs
- In critically ill patients, withdrawal of immunosuppression could be done while converting those patients to hydrocortisone/solumedrol.
- This approach may improve viral clearance but could lead to immune reconstitution and kidney's rejection

- It should be considered that reducing immunosuppression may exacerbate inflammation, so this approach should be cautioned in the absence of anti-inflammatory agents
- In some patients, tacrolimus reduction may be preferred over complete withdrawal because of direct alleged CNI antiviral properties or CNI anti-inflammatory action.
- Pending the results of clinical studies, CNI withdrawal vs. reduction may be established on a case-by-case basis depending on the severity of pneumonia.

Living Kidney Donation During the COVID-19 Pandemic

- In countries with widespread community transmission, living-donor kidney programs have been temporarily suspended.
- In countries where community transmission is lower, living donations should not be performed if the donor or recipient have lived in a place with high incidence or have been in contact with confirmed or suspected COVID-19 patient within 14 days

Donation From Deceased Donors During the COVID-19 Pandemic

 In countries with sporadic COVID-19 infection, deceased donor transplants should continue. However, donors at risk of infection should not be accepted since RNAemia was reported in at least 15% in one case series, and, transmission from the donor is possible The Columbia University Kidney Transplant Program's clinical practice has suggested to delay reintroduction of these drugs for up to 2 weeks after discharge, recognizing that prolonged reduction of immunosuppression therapy increases the risk of allograft rejection

- Similarly, Alberici et al., in a single center observational study which was conducted in Italy, described a rapid clinical deterioration associated with chest radiographic deterioration and escalating oxygen requirement in 20 kidney transplant recipients with SARS-CoV-2 pneumonia.
- Thus, in this limited cohort of long-term renal transplant patients, SARS-CoV-2 induced pneumonia is characterized by a high risk of renal progression and a significant mortality rate. Despite on average a relatively benign onset of the disease, a large rate of the patients showed worsening chest radiographs and consequently needed an escalation of the supplemental oxygen.
- Of note, 25% of the patients died espite an aggressive approach to immunosuppression withdrawal and early administration of antiviral therapy

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COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium

Paolo Cravedi 🖾, Suraj S. Mothi, Yorg Azzi, Meredith Haverly, Samira S. Farouk, María J. Pérez-Sáez, Maria D. Redondo-Pachón, Barbara Murphy ... See all authors 🗸

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Enver Akalin and Leonardo V. Riella are co-senior authors. Paolo Cravedi and Suraj Sarvode Mothi are co-first authors.



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COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium

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AJT

• Kidney transplant recipients may be at a high risk of developing critical coronavirus disease 2019 (COVID-19) illness due to chronic immunosuppression and comorbidities.

• We identified hospitalized adult kidney transplant recipients at 12 transplant centers in the United States, Italy, and Spain who tested positive for COVID-19

- Among 9845 kidney transplant recipients across centers, 144 were hospitalized due to COVID-19 during the 9-week study period.
- Of the 144 patients, 66% were male with a mean age of 60 (±12) years, and 40% were Hispanic and 25% were African American. Prevalent comorbidities included hypertension (95%), diabetes (52%), obesity (49%), and heart (28%) and lung (19%) disease. Therapeutic management included antimetabolite withdrawal (68%), calcineurin inhibitor withdrawal (23%), hydroxychloroquine (71%), antibiotics (74%), tocilizumab (13%), and antivirals (14%). During a median follow-up period of 52 days (IQR: 16-66 days), acute kidney injury occurred in 52% cases, with respiratory failure requiring intubation in 29%, and the mortality rate was 32%.

• The 46 patients who died were older, had lower lymphocyte counts and estimated glomerular filtration rate levels, and had higher serum lactate dehydrogenase, procalcitonin, and interleukin-6 levels.

• In sum, hospitalized kidney transplant recipients with COVID-19 have higher rates of acute kidney injury and mortality.

Clinical outcomes

- The most common symptoms on admission were fever and dyspnea (67%), followed by myalgia (53%) and diarrhea (38%)
- During a median follow-up of 52 days (IQR: 16-66 days) after the diagnosis of the first COVID-19 patient, 74 patients developed acute kidney injury (51%), 42 patients required mechanical ventilation (29%), and 46 patients had died, totaling 32% mortality in this cohort. Twenty-two of the patients who entered the ICU died (51%).
- The median time from illness onset (i.e., before admission) to discharge was 22 days (IQR 15-35 days), whereas the median time to death was 15 days (IQR: 8-22 days; Table <u>1</u>).
- Extracorporeal membrane oxygenation was used in 3 patients, none of whom survived.

Risk factors associated with death from COVID-19

- There was no difference in mortality across the transplant centers. Patients who died were older than survivors (66 vs 60 years old; *P* < .001), with 71% of patients over the age of 60 among nonsurvivors .
- There was no significant difference in outcomes between recipients of organs from living or deceased donors or between patients with < 1 year since transplant compared with those with longer time since transplant
- Time from onset of symptoms to admission was slightly shorter in patients who died.
- Neither race, comorbidities, induction therapy with depleting agents, maintenance immunosuppression, nor therapy with Renin Angiotensin System inhibitors differed significantly between survivors and nonsurvivors

Presentation and laboratory results according to mortality from COVID-19

- The respiratory rate at admission was significantly higher in non survivors compared with survivors and diarrhea was less frequent in non survivors (23.9% vs 44.9%).
- None of the other clinical characteristics at presentation differed significantly between the 2 groups.
- Major laboratory markers were tracked from illness onset. Lymphopenia (<0.8) was present in 42% of patients.
- Baseline lymphocyte count was significantly higher in survivors than in non survivors (1.2 vs 0.7, P = .004) as well as estimated glomerular filtration rate (eGFR; 53 vs 38 mL/min).

Treatment of COVID-19 in kidney transplant recipients

- In most cases, mycophenolate (MMF/MPA) or everolimus was reduced or discontinued (68%), whereas calcineurin inhibitor was discontinued in 32 patients (23%).
- There was no significant association between immunosuppression withdrawal and mortality.
- Most patients received hydroxychloroquine (71%) and antibiotics (74%), and a smaller subset of patients received tocilizumab (13%) or antivirals (14%).
- There was no significant difference in mortality among different treatments of COVID-19 with the exception of a slightly greater use of antibiotics in nonsurvivors.

Predictors of mortality

- In univariable analysis, the odds of in-hospital death was higher in older patients and patients with higher respiratory rates, LDH, IL-6, and procalcitonin levels, whereas mortality risk was lower in patients with diarrhea or higher eGFR levels.
- In addition to age, we found that higher respiratory rate, lower eGFR, and higher IL-6 at admission were associated with increased odds of death

REVIEW



COVID-19 and the kidney: what we think we know so far and what we don't

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Abstract

The novel coronavirus disease infection (COVID-19) outbreak that was declared a global pandemic in March 2020 had led to an internationally variable but concerning incidence of COVID-associated acute kidney injury (AKI), with prevalence reported as high as 46% in large cohorts of hospitalized patients. Variability in AKI may be explained by differences in traditional risk factors for AKI, heterogeneity among patient cohorts, and differences in racial and ethnic groups. Further, AKI requiring kidney replacement therapies (KRT) has been associated with increased mortality. Proposed mechanisms of kidney injury include direct viral-induced tubular or glomerular injury, sepsis-associated AKI, and thrombotic disease. Kidney pathology include acute tubular injury, glomerular fibrin thrombi, pigmented tubular casts, and collapsing focal segmental glomerulosclerosis. "Viral-like" particles have been observed in renal samples at electron microscopy and viral RNA has been identified in both glomerular and tubular compartments of kidney specimens, but the link between viral presence and injury remain unclear. Though the link between AKI and poor outcomes is clear, prevalence and outcomes of COVID-19 in patients with chronic kidney disease and end stage kidney disease has not yet been reported. In patients on immunosuppres-

- Kidney transplant recipients appear to be at higher risk for hospitalization and death from COVID-19.
- Similar to incidence rates of AKI, reported mortality rates in this population have varied and as high as 28% .
- There is an absence of consensus about how to adjust immu-nosuppression in Covid-19 kidney transplant recipients.
- While immunosuppression may prevent an effective anti-SARS-CoV-2 T cell response, it may also allow controlling inflammatory response that is, at least in part, responsible for COVID-19 related mortality.
- Calcineurin inhibitors, the backbone of the majority of immunosuppression regi-mens, have shown in vitro activity against coronaviruses—though clinical data are lacking .
- While most centers reduce immunosuppression, approaches vary significantly from institution to institution

Conclusions

- SARS-CoV-2 effects on the kidney and in patient with underlying kidney disease is not well-characterized.
- Preliminary data has indicated that previous kidney disease could represent a risk factor, especially in elderly patients, for a more severe disease course.
- SARS-CoV-2 infects the kidneys and may induce acute kidney injury.
- While there is no current specific therapy, many drugs both antiviral and/or antiinflammatory are being actively tested in randomized trials.
- Further studies are necessary to better understand disease pathology, acute kidney injury associated with infection, long-term renal consequences, and potential therapies.
- Rigorously controlled interventional studies and international registry analyses will be crucial to define risk factor and the best therapeutic approaches to resolving COVID-19 disease outcomes.

Recommendation

- Until more data is available, the rules to prevent viral infection in the general population apply to transplant patients (hand hygiene, sanitization, social distancing, and avoiding areas where infected patients could be present).
- Transplant patients with potential COVID-19 infection should not access the transplant center due to risk of viral spread.

<u>COVID-19 in CKD patients – part KT patients- in</u> <u>Alzahra- hospital center-Isfahan university of</u> <u>medical sciences</u>

 In Alzahra center (Isfahan Providence): about 60 patients admitted to the hospital from March to November 2020, 16 patients died, 5 patients with graft failure, 5 patients with loss of eGFR from baseline. unpublished data-





