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RESEARCH LETTER

COVID-19 and solid organ transplant outcomes

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread out from a single city in China to most of the world. Patients found to be at higher risk for infection and adverse outcome include those with comorbid conditions and the elderly. Until recently, data on immunocompromised kidney transplant patients have been lacking. Given their diminished T-cell immunity, transplant recipients are expected to be at higher risk for severe bacterial and viral infections. This would suggest that they are at higher risk for infection and mortality from coronavirus disease 2019 (COVID-19). However, recent publications report great variations in the clinical course and mortality of COVID-19 in solid organ transplant recipients [1–9]. It is unclear whether these differences are related to study methods, treatment choices or variables associated with patient populations among different transplant centers. Studies with low to no mortality may support a beneficial immunosuppressive effect on the cytokine storm described with COVID-19, whereas those with high mortality rates may further enhance the deleterious association of immunosuppression and infections.

To better understand the true risk of COVID-19 in transplant recipients, we sought to collect and summarize existing experiences. We performed a PubMed search for all published manuscripts that included kidney transplantation and COVID-19. We excluded studies with fewer than five kidney transplant recipients, and those without data reported. We reviewed dates of publication, number of patients, types of solid organ transplantation including kidney transplantation, patient demographics, comorbid conditions, baseline immunosuppression, changes in immunosuppression, presenting symptoms, hospital course, treatments administered, follow-up time and patient mortality.

Of 13 articles from February to 1 May 2020, 4 were excluded for having fewer than five kidney transplant recipients. A summary of the nine analyzed manuscripts is detailed in Table 1. Two studies [6, 8] included kidney, non-kidney and combined kidney and other organ transplantations. Most studies included patients with a median age in the 50s with primary comorbidities of hypertension and diabetes (in addition to the primary organ failure). The majority of patients were male. COVID-19 diagnosis was confirmed via laboratory testing in all studies. Calcineurin inhibitors, antimetabolites and prednisone were among the types of immunosuppression used. The majority of patients included in the studies were on tacrolimus, mycophenolate and prednisone. The presenting symptoms were usually fever, cough and dyspnea, and less commonly diarrhea. Immunosuppression was either reduced or discontinued upon diagnosis in all studies. Not all authors reported on intensive care unit admission and intubation, potentially introducing a bias in the severity of illness.

All studies published after March 2020 utilized hydroxychloroquine in the majority of COVID-19-positive transplant recipients. Azithromycin, remdesivir, leronlimab, lopinavir/ritonavir, darunavir, oseltamivir and tocilizumab were also used. All studies described hospitalized patients. A third of the reports also included outpatients [3, 6, 7]. The median [interquartile range(IQR)] follow-up time was ∼3 weeks for most studies (7–29 days). Mortality ranged from 0% to 30%.

All studies (except Study [1]) that reported patient mortality under 20% did not report follow-up data or reported a median follow-up <10 days. In general, larger studies also tended to have a higher mortality. At the time of our analysis, we observed a higher mortality among more recent reports.

In summary, the available literature suggests that presentation of COVID-19 in transplant recipients is similar among transplant centers around the world. Immunosuppression strategies are also similar and revolve around reducing immunosuppression. Treatment strategies vary; however, all studies utilized some antiviral or anti-inflammatory agent. Differing outcomes may therefore be related to small number of cases, potentially varying acuities of illness, and short (or not reported) follow-up periods being associated with lower mortality. Given that the cytokine storm occurs later in the course of COVID-19, it is plausible that mortality may increase with follow-up. When excluding short or missing follow-up, recent mortality appears to be between 20% and 30%, which suggests that transplant recipients have a higher mortality than the non-immunocompromised population.

It is of utmost importance to understand these risks before proceeding with transplantation in the current era of COVID-19. Factors to be considered include the potential for improved survival and enhanced quality of life, the risk of SARS-CoV-2

Table 1. Summary of COVID-19 in Transplantation Studies from February to May 2020

Studies	Zhang *et al.* [1]	Zhu *et al.* [2]	Banerjee *et al.* [3]	Alberici *et al.* [4]	Columbia University Kidney Transplant Program [5]	Fernandez-Ruiz *et al.* [6]	Akalin *et al.* [7]	Pereira *et al.* [8]	Nair *et al.* [9]
Date accepted for publication	March 20	March 23	March 27	April 3	April 6	April 16	April 24	April 24	April 29
Number of patients	5	10	7	20	15	18	36	90	10
Organ transplanted	Kidney	Kidney	Kidney	Kidney	Kidney	Kidney 8, liver 6, heart 4	Kidney	Kidney 46, lung 17, liver 13, heart 9, heart-kidney 3, liver-kidney 1, pancreas-kidney 1	Kidney
Age, years	38 (38–47)	50 (32–54)	54 (45–69)	59 (51–64)	51 (28–72)	71 (64–75)	60 (32–77)	57 (46–68)	57 (47–67)
Male gender, %	80	80	57	80	67	77.8	72	59	60
Time from transplant	352 days (170–929)	6–12 months	3 to ≥1 year	13 years (9–20)	4.1 years (3.2–9.8)	9.3 years (6.3–16.5)	No info	6.64 years (2.87–10.61)	7.7 years (3.5–12.6)
Comorbidities, %									
HTN	40	50	86	85	–	56	94	64	100
DM	20	–	43	15	–	–	69	46	80
CKD	–	–	–	–	–	–	–	63	–
CLD	–	–	–	–	–	–	–	19	–
CHD	–	20	–	15	–	17	17	–	–
Cirrhosis	–	–	–	–	–	28	–	–	–
Baseline immuno-suppression, %									
Tacrolimus	80	90	86	95	93	56	97	86	90
Cyclosporine	–	10	–	–	–	17	–	–	–
MMF/MPA	100	90	71	70	80	61	86	72	100
Prednisone	–	70	71	65	67	67	94	59	70
mTOR	–	–	–	10	–	22	–	7	20
Belatacept	–	–	–	–	13	–	–	6	–
Presenting symptoms, %									
Fever	–	90	71	100	87	83	58	70	90
Cough	100	90	57	50	60	67	53	60	80
Dyspnea	–	90	86	5	27	61	44	43	30
Diarrhea	–	30	14	15	20	22	22	31	20
Fatigue	60	90	–	–	27	–	–	28	50
ICU admission	0	–	57	20	–	11	–	34 (23/68)	50
Intubation/ mechanical ventilation	0	0	29	10	27	11	39 (11/28)	35 (24/68)	44 (4/9)
Immuno-suppression reduced/ discontinued	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment(s), %									
HCQ	–	–	–	95	87	72,[a] 8 in combo with LPV/r	86 (24/28)	91 (62/68)	100 (9/9)
Azithromycin	–	–	–	–	60	–	46 (13/28)	66 (45/68)	100 (9/9)
Remdesivir	–	–	–	–	–	–	–	3 (2/68)	–
Tocilizumab	–	–	–	30	7	6	7 (2/28)	21 (14/68)	–
Leronlimab	–	–	–	–	–	–	21 (6/28)	–	–
Oseltamivir	100	20	14	–	–	–	–	–	–
Follow-up, days	29 (27–31)	–	–	–	7 (3–11)	18 (14.5–22)	21 (14–28)	20 (14–24)	25 (11–26)
Mortality	0	10	14	25	7	28	28	24	30

[a]All data presented as median (IQR) unless otherwise noted. CHD: coronary heart disease; CKD: chronic kidney disease; CLD: chronic lung disease; DM: diabetes; ICU: intensive care unit; HCQ: hydroxychloroquine; HTN: hypertension; LPV/r: lopinavir/ritonavir; MMF: mycophenolate mofetil; MPA: mycophenolic acid; mTOR: mammalian target of rapamycin; –, not recorded.

infection in the transplant population when compared with in-center dialysis, and the increased morbidity and mortality associated with COVID-19 in the setting of transplantation. Ongoing studies reporting multi-center data may provide us with more robust information.

CONFLICT OF INTEREST STATEMENT

KDJ is a consultant for Astex pharmaceuticals and Natera. All other authors have no conflict of interests to declare.

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Oral potassium binders: increasing flexibility in times of crisis

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Successful and safe management of hyperkalaemia became more pertinent during the coronavirus disease 2019 (COVID-19) pandemic, as nephrologists grappled with delayed transfer of patients into renal centres, difficulties providing short-term haemofiltration in intensive care units (ICUs), minimizing hospital visits and reorganizing haemodialysis (HD) services to facilitate isolated COVID-19 areas. With an unprecedented demand, the need to preserve ICU beds, and an often-reduced work force, changes in medical practice were required.

COVID-19 has particularly affected renal patients, with 4360 cases and 1403 deaths in adult renal patients across the UK and Northern Ireland as of 17 June 2020 [1]. Among 1530 HD patients at our centre in North West London, there were 300 cases and 94 deaths [2]. These statistics are unsurprising with COVID-19 risk factors, including advanced age, hypertension, diabetes mellitus and vascular disease, and being of Black, Asian or minority ethnic origin highly prevalent in renal patients.

With a high number of admissions and the need to alter outpatient pathways, renal services were overwhelmed. In an effort to protect patients admitted to non-renal centres and reduce ICU admissions, nephrologists provided remote support to manage serum potassium.

Standard management includes the use of insulin/dextrose, salbutamol and sodium bicarbonate, but their use risks hypoglycaemia, tachyarrhythmias and fluid overload [3, 4]. Newer agents such as sodium zirconium cyclosilicilate (SZC), an inorganic crystalline compound, and Patiromer, a cation exchange polymer, are oral, non-absorbed potassium binders, licenced within the UK for acute and chronic hyperkalaemia in adults other than those on renal replacement therapy (RRT) [5]. Furthermore, the Phase IIIb DIALIZE trial showed SZC to be safe in HD patients, with trials under way to determine the efficacy of Patiromer. Their use will therefore increase over time [6, 7].