Impact of COVID-19 infections among kidney transplant recipients

Dear Editor,

More than 2 years since the start of the COVID-19 pandemic, cases continue to climb despite global efforts at viral control. This is largely driven by the emergence of viral variants. In the later part of 2021, the Delta variant was the predominant variant circulating globally, and was associated with increased infectivity, transmissibility, reduced vaccine response, and reduced susceptibility to monoclonal antibodies.¹⁻³

In Singapore, despite having a robust test-trace-isolate strategy since the start of the pandemic, and one of the highest vaccination rates in the world with more than 80% of our population being fully vaccinated, the Delta variant has managed to “break through” our control measures, causing an exponential increase in the number of COVID-19 cases since the start of September 2021.⁴ In addition, as restrictions loosen for practical and economic reasons, it is inevitable that COVID-19 infections in the immunocompromised patients (including kidney transplant recipients) will increase. Prior to September 2021, there were no reported COVID-19 infections in kidney transplant recipients on our follow-up. However, within the first few weeks of lifting restrictions (1 September to 15 October 2021), 12 of our patients were infected. Among them, 10 were treated at Singapore General Hospital and are described in this report. We had existing approval by the ethics committee of the institution to evaluate longitudinal outcomes in kidney transplant.

Patient demographics, clinical presentation and outcomes are described in Table 1 (also Table S1 of Supplementary Materials in the online version of this article). Their median age was 61.5 (range 52–65) years. Most patients acquired COVID-19 from the community—6 (60%) from close contacts (either household or social contacts), 1 (10%) nosocomial transmission, and 3 (30%) unlinked. Seven (70%) patients had received at least 2 doses of the Pfizer BNT162b2 vaccine, and only 2 (28.6%) of these 7 had a serological response. The median time to infection from the second dose of vaccine was 137 (39–164) days. Three (30%) patients were unvaccinated, 1 of whom had prior COVID-19 infection in India.

Most patients (80%) developed mild to moderate infections; the 2 (20%) patients who developed severe

infection required only supplementary oxygen therapy via nasal prongs. None developed graft dysfunction as defined by >25% increase in baseline creatinine, and none were reinitiated on dialysis. Eight (80%) patients were admitted within the first 7 days of illness, and received early COVID-19 specific therapeutics. Five (50%) received sotrovimab monotherapy, 6 (60%) remdesivir, 1 (10%) remdesivir/dexamethasone, and 1 (10%) received sotrovimab on admission, followed by remdesivir/dexamethasone when she developed type 1 respiratory failure. Patients who developed lymphopaenia and/or were symptomatic with moderate to severe disease had their anti-metabolite suspended promptly. Calcineurin inhibitors and mechanistic target of rapamycin (mTOR) inhibitors doses were maintained; patients with mild-to-moderate disease were maintained on their regular prednisolone doses.

Four (40%) patients developed bacterial co-infections (2 urinary tract infections and 2 pneumonia). None developed cytomegalovirus reactivation. All our patients have recovered and are discharged. For de-isolation purposes, we repeated nasopharyngeal swabs for SARS-CoV-2 polymerase chain reaction (PCR) and de-isolated patients when the cycle threshold of >30 was achieved. None demonstrated viral rebound based on serial PCR testing. Therefore, the theoretical risk of new COVID-19 variants developing in our cohort with stable immunosuppression was deemed negligible. The median time to meet criteria for de-isolation is 21 (17–22) days.

In our series, there are several key observations.

Firstly, in spite of our best efforts to mitigate the risk of COVID-19 through multipronged approach by educating our patients on public health measures (universal masking, safe distancing and good hand hygiene) in April 2020; conducting webinars on the importance of COVID-19 vaccination in transplant recipients in February 2021; and rolling out a mass vaccination programme with 90% uptake among 867 patients known to us, zero COVID-19 acquisition for our patients is impossible now that COVID-19 is endemic.

Secondly, consistent with published data, vaccine responses following a 2-dose mRNA COVID-19 vaccination series in our transplant recipients are poor,

Table 1. COVID-19 in kidney transplant recipients: Transplant history, clinical presentation and outcomes

Patient no.	1	2	3	4	5	6	7	8	9	10
Tx history										
Indication for Tx	Chronic GN (DDRT)	Ig A nephropathy (LDRT)	DM nephropathy (DDRT)	DM nephropathy (LDRT)	Chronic GN (LDRT)	Chronic GN (DDRT)	DM nephropathy (ABOi LDRT)	HTN nephropathy (LDKT)	HTN nephropathy (DDRT)	Chronic GN (DDRT)
Induction IS	BAS	MP	BAS	Unknown ^a	Unknown ^a	BAS	ATG	Unknown ^a	BAS	Unknown ^a
Maintenance IS	Pred	MPA, FK, Pred	MMF, FK, Pred	MMF, CsA, Pred	Aza, CsA, Pred	FK, Pred	MPA, FK, Pred	MMF, FK, Pred	EVR, Pred	Aza, CsA, Pred
Time from Tx to C+, months	136	10	47	216	249	30.5	21.5	239	25	372
COVID-19 immunity										
COVID-19 vaccination	No	No	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	No	Pfizer (3 doses)	Pfizer (2 doses)
Days from last vaccine dose to C+	NA	NA	137	129	35	175	39	NA	164 (2 nd dose) 7 (3 rd dose)	154
SARS-CoV-2 Ig G (RBD) ^b , IU/mL	NA	592	<50	<50	286.8	1,657.3	<50	<50	<50	NA
Clinical parameters										
Sx at presentation	Fever, cough, dyspnoea	Asymptomatic	Cough, myalgia, pleuritic chest pain	Fever, rhinorrhoea	Cough, sore throat	Fever, rhinorrhoea, diarrhoea, cough, sore throat	Fever, cough, sore throat, anosmia	Fever, sore throat, anosmia	Asymptomatic	Initial URTI, presented late with progressive dyspnoea
Day of illness on admission ^c	D 0	D 2	D 8	D 1	D 4	D 7	D 1	D 3	D 7	D 16
Severity of disease on admission ^d	Moderate (Pneumonia ^e)	Asymptomatic	Moderate (Pneumonia ^e)	Moderate (Pneumonia ^e)	Moderate (Pneumonia ^e)	Mild (URTI)	Mild (URTI)	Moderate (Pneumonia ^e)	Moderate (Pneumonia ^e)	Severe (Pneumonia ^e)
Duration of Sx, days	9	Asymptomatic	16	5	7	7	6	5	Asymptomatic	24
Viral shedding ^f , days	21	8	21	23	21	22	21	16	12	25
Nadir abs. Lf, x10 ⁹ /L (Day of illness)	2.04 (D 11)	1.26 (D 2)	0.47 (D 9)	0.27 (D 5)	1.87 (D 5)	0.79 (D 9)	0.50 (D 1)	0.05 (D 3)	1.04 (D 7)	0.52 (D 16)
Progression of COVID-19	No	No	Yes (TIRF)	No	No	No	No	No	No	Yes (TIRF)
Day of deterioration ^g	NA	NA	D 13 illness	NA	NA	NA	NA	NA	NA	D 17 illness

Table 1. COVID-19 in kidney transplant recipients: Transplant history, clinical presentation and outcomes (Cont'd)

	1	2	3	4	5	6	7	8	9	10
Clinical parameters										
Peak O ₂ requirements	RA	RA	2L NP	RA	RA	RA	RA	RA	RA	3L NP
Day of deterioration ^a	NA	NA	D 13 illness	NA	NA	NA	NA	NA	NA	D 17 illness
Peak O ₂ requirements	RA	RA	2L NP	RA	RA	RA	RA	RA	RA	3L NP
COVID-19 management										
COVID-19-specific treatment (no. of days)	Sotrovimab Rem (5)	Sotrovimab	Sotrovimab Rem (5) Dexa (5)	Sotrovimab Rem (10)	- Rem (5)	Nil	Sotrovimab Rem (3)	Sotrovimab Rem (3)	- Rem (3 days, followed by another 5 days from D 11 illness)	- Rem (3) Dexa (3)
Adjustment of IS	Nil	Nil	MMF stopped	MMF dose reduced	Aza stopped	Nil	MPA stopped	MMF stopped	Nil	Aza stopped
Final disposition										
C+ severity at discharge	Moderate	Asymptomatic	Severe	Moderate	Moderate	Mild	Mild	Moderate	Moderate	Severe
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered

ABOi: ABO incompatible; abs: absolute; ATG: anti-thymocyte globulin; Aza: azathioprine; BAS: basiliximab; C+: COVID-19 infection; CsA: ciclosporin; CT: cycle threshold; DDRT: deceased donor renal transplant; Dexa: dexamethasone; DM: diabetic; EVR: everolimus; FK: tacrolimus; GN: glomerulonephritis; HTN: hypertensive; ICU: intensive care unit; IS: immunosuppression; LDRT: living donor renal transplant; Lf: lymphocyte; MMF: mycophenolate mofetil; MP: methylprednisolone; MPA: mycophenolic acid EC; NA: not available; NP: nasal prongs; Pred: prednisolone; RA: room air; RBD: receptor binding domain; Rem: remdesivir; Sx: symptoms; TIRF: type 1 respiratory failure; Tx: transplant; URTI: upper respiratory tract infection; ;

^a This was a transplant performed at an overseas transplant centre and we did not have information with regard to the induction immunosuppression used.

^b Serological testing against COVID-19 was performed at the point of admission to our hospital, prior to the receipt of any COVID-19 specific therapeutics.

^c D1 of illness is defined as the onset of clinical symptoms OR the day of first positive COVID-19 test (either by polymerase chain reaction [PCR] or antigen testing), whichever is earlier.

^d Severity of disease is based on the classification by the National Institutes of Health. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: <https://www.covid19treatmentguidelines.nih.gov/>. Accessed on 17 October 2021.

^e This refers to radiological evidence of pneumonia as characterised by chest infiltrates.

^f Duration of viral shedding is defined as the time taken for the SARS-COV-2 PCR CT to reach >30

^g The day of clinical deterioration is in relation to onset of clinical illness OR the first positive COVID-19 test (either by PCR or antigen testing).

at only 28.6%.⁵ Most patients had SARS-CoV-2 immunoglobulin G receptor bonding domain level of <50IU/mL. There was only 1 patient with antibody levels >1,000IU/mL. Interestingly, his infection was mild, and required only symptomatic treatment. Intuitively, additional vaccine doses may improve vaccine responses, and this has also been published. With a third dose mRNA vaccine, serological responses improved significantly from 40% to 68%; a 3-dose mRNA primary vaccination series (at a minimum) is now recommended for transplant recipients.⁶ Even so, post-vaccination seroprotective thresholds are not defined, and waning immunity post-vaccination is increasingly being recognised.^{7,8} As such, routine serological testing post-vaccination in transplant recipients is not standard of care, and should not be routinely performed.

With regard to outcomes, most of our patients had mild-to-moderate infections. Only 2 (20%) developed severe pneumonia but they never required critical care. This is in contrast to reported data from the earlier phases in the pandemic where approximately 40% of solid organ transplant recipients required intensive care.⁹ There are 2 possibilities. Perhaps a 2-dose mRNA COVID-19 vaccination series could still have induced T-cell responses (not assessed by serological assays) and this reduced the risk of progression to severe disease.^{5,10} However, our unvaccinated patients (albeit small numbers) also had relatively good outcomes. Therefore, a more likely reason is that we have adopted a more aggressive approach by admitting all known COVID-19 infected patients for consideration of monoclonal antibody therapy (in sero-negative patients, or those with relatively lower antibody titres) and early treatment with remdesivir where appropriate.^{11,12} This strategy is different from how we treat bacterial infections, where therapeutics are usually reserved for the sick or symptomatic. We would also like to highlight that even in mildly symptomatic COVID-19 infected transplant recipients, there was radiological evidence for pneumonia early in their illness, supporting the early administration of remdesivir.¹¹ In addition, titration of immunosuppressants by our transplant physicians (in particular the early suspension of the anti-metabolites in patients who are lymphopaenic or those with progressive disease) was useful.¹¹ We postulate that the efforts to prevent viral attachment and replication in our patients may have mitigated the downstream inflammatory responses seen in COVID-19.^{11,12}

During the Delta outbreak, we recommend early evaluation and treatment of COVID-19 infected kidney transplant recipients in an inpatient setting, where they can receive early access to therapeutics (which are only available parenterally) and be closely monitored for complications. Moving forward, the model of care (e.g. management in acute hospital versus dedicated community care facility vs home recovery with telemedicine support) depends on several factors: (1) infectivity and virulence of the circulating SARS-CoV-2 virus, (2) medical complexity of the patients, (3) vaccine efficacy in solid organ transplant recipients, (4) access to approved therapeutics, (5) prevailing COVID-19 infection prevention goals and strategies, (6) capacity of our healthcare systems (including hospital bed availability, manpower availability, infrastructure, and auxiliary support for community care and telemedicine) and (7) psychological-social-cultural expectations of Singapore residents. We will have to continually modify our strategies based on pandemic situation, available resources, and emerging scientific data that inform care.

Finally, an ounce of prevention is worth a pound of cure. Public health measures, and vaccination of our patients and their close contacts, remain key pillars of the global COVID-19 control strategy.

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REFERENCES

1. GISAIID. Tracking of Variants. Available at: <https://www.gisaid.org/hcov19-variants/>. Accessed on 17 October 2021.
2. World Health Organization. Weekly epidemiological update on COVID-19 - 13 October 2021, 13 October 2021. Available at: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-october-2021>. Accessed on 19 October 2021.
3. Ong SWX, Chiew CJ, Ang LW, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta). *Clin Infect Dis* 2021:ciab721.
4. Ministry of Health, Singapore. COVID-19 Situation Report. Available at: <https://covid19.moh.gov.sg>. Accessed on 18 October 2021.
5. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA* 2021;325:2204-6.

6. Kamar N, Abravanel F, Marion O, et al. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N Engl J Med* 2021;385:661-2.
7. Ison MG, Blumberg E, Halasa N, et al. Antibodies, boosters, and optimizing SARS-CoV-2 vaccines for transplantation: A call for more research. *Am J Transplant* 2021.
8. Goldberg Y, Mandel M, Bar-On YM, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. *N Engl J Med* 2021;385:e85.
9. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant* 2020;20:1800-8.
10. Aslam S, Adler E, Mekeel K, et al. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. *Transpl Infect Dis* 2021:e13705.
11. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: <https://www.covid19treatmentguidelines.nih.gov/>. Accessed on 17 October 2021.
12. Dhand A, Lobo SA, Wolfe K, et al. Casirivimab-imdevimab for Treatment of COVID-19 in Solid Organ Transplant Recipients: An Early Experience. *Transplantation* 2021;105:e68-9.

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