

Outcomes of COVID-19 infection in patients on dialysis and kidney transplant recipients: A single-centre audit

Dear Editor,

Patients with end-stage kidney disease (ESKD) are at increased risk of adverse outcomes following COVID-19 infection. Their vulnerability stems from multiple factors including kidney failure, comorbid illnesses, close contact in the haemodialysis centre, and transplant immunosuppression. European registry data in the pre-vaccination era report a COVID-19 mortality rate of 20% among patients on dialysis and 19.9% in kidney transplant recipients, with transplant recipients having 1.28 times the mortality risk of matched dialysis patients.¹ More recent studies have reported mortality rates of 7–20% among vaccinated patients on dialysis or transplant recipients.^{2–4}

During the COVID-19 pandemic, the Department of Renal Medicine at the Singapore General Hospital performed an Institutional Review Board-approved audit (Singhealth CIRB 2021/2823) to monitor COVID-19 caseload and treatment outcomes. This letter presents this important data to prepare for the next pandemic.

All patients on dialysis or transplant recipients treated for SARS-CoV-2 infection at the Singapore General Hospital from 1 September 2021 to 30 April 2022, and who had a positive SARS-CoV-2 polymerase chain reaction with cycle threshold <25, were included. Patients aged <18 years, who required only temporary dialysis, or who initiated dialysis or underwent transplantation during the same admission were excluded. Cases were classified as occurring during the delta or omicron wave based on the cut-off date of 1 December 2021 on which the Omicron variant was first reported in Singapore.⁵ The primary endpoint was inpatient mortality. Secondary endpoints include mechanical ventilation and allograft dysfunction in transplant recipients.

Deidentified patient information was collected from medical records. SPSS Statistics version 28 (IBM Corp, Armonk, NY, US) was used for data analysis. Differences in baseline characteristics and outcomes were compared between patients on dialysis and kidney transplant recipients using chi-square, Fisher's Exact test and t-test as appropriate. The association between baseline characteristics and mortality was explored using binary logistic regression. Multivariate logistic regression was used to investigate the association between patient characteristics, clinical factors, and admission investigations with mortality. *P* values <0.05 were considered significant.

The audit included 491 patients: 259 patients on dialysis (247 haemodialysis, 12 peritoneal dialysis) and 232 transplant recipients. Transplant recipients were younger than patients on dialysis (age, mean [standard deviation], 65.6 [12.4] versus 57.6 [10.9], *P*<0.001), and had lower Charlson comorbidity indices (7.21 [2.43] vs 3.71 [1.51], *P*<0.001). Overall, 441 patients (89.8%) were fully vaccinated with ≥2 doses of a COVID-19 vaccine, of which 286 patients (58.2% of total) had also received a booster dose. Transplant recipients were more likely than patients on dialysis to be fully vaccinated (94.8% vs 85.3%, *P*<0.001) or have had a booster dose (78.0% vs 40.5%, *P*<0.001), yet were more likely to have inadequate immunoglobulin G (IgG) antibodies (<500 BAU/mL) against the receptor-binding domain of the SARS-CoV-2 virus (56.3% vs 32.7%, *P*<0.001) at the time of infection.

Cohort mortality was 2.9%. Transplant recipients had lower mortality (0.4%) than patients on dialysis (5.0%) odds ratio [OR] 0.082, 95% confidence interval [CI] 0.011–0.631, *P*=0.002). Mortality was higher during the delta (5.1%) than the omicron wave (2.1%), but this did not reach statistical significance (OR 2.48, 95% CI 0.840–7.30, *P*=0.11). Mechanical ventilation was required in 3.1% of all patients, less often in transplant recipients (1.3%) than in patients on dialysis (4.6%) (OR 0.271, 95% CI 0.075–0.972, *P*=0.037). Thirty-two transplant recipients (13.8%) had allograft dysfunction, with 1 graft loss (0.4%).

On univariate analysis, baseline characteristics associated with mortality include: patient on dialysis, age (per year increase, OR 1.12, 95% CI 1.06–1.19, *P*<0.001), and higher Charlson comorbidity index (per point increase, OR 1.30, 95% CI 1.09–1.55, *P*=0.003). Admitting investigations associated with mortality include consolidation on chest X-ray (OR 4.26, 95% CI 1.39–13.0, *P*=0.011), higher white cell count (per $1 \times 10^9/L$ increase, OR 1.39, 95% CI 1.23–1.56, *P*<0.001), higher C-reactive protein (per 1mg/L increase, OR 1.48, 95% CI 1.28–1.73, *P*<0.001), and lower albumin (per 1g/L decrease, OR 1.15, 95% CI 1.06–1.24, *P*<0.001). The 4C score predicted mortality in this cohort (per 1 point increase, OR 1.90, 95% CI 1.41–2.56, *P*<0.001). Vaccination status or SARS-CoV-2 antibody levels were not significantly associated with mortality.

On multivariate analysis, independent predictors of mortality were age (per year increase, OR 1.14,

Table 1. Characteristics and outcomes of COVID-19 infection.

		Dialysis (n=259)	Transplant (n=232)	P value
Baseline characteristics				
Age	mean ± SD	65.6 ± 12.4	57.6 ± 10.9	<0.001 ^a
Male sex	n (%)	157 (60.6)	125 (53.9)	0.144
Aetiology of kidney failure				
- Diabetes	n (%)	141 (55.3)	28 (12.1)	
- Glomerulonephritis	n (%)	53 (20.8)	166 (71.6)	
- Hypertension	n (%)	39 (15.3)	54 (23.3)	
- Polycystic kidney disease	n (%)	7 (2.7)	9 (3.9)	
- Others	n (%)	15 (5.9)	14 (6.0)	
Duration on dialysis or transplant, years	mean ± SD	4.52 ± 4.77	12.4 ± 9.37	<0.001 ^a
Charlson Comorbidity Index	mean ± SD	7.21 ± 2.43	3.75 ± 1.51	<0.001 ^a
Fully vaccinated (≥2 doses)	n (%)	221 (85.3)	39 (94.8)	<0.001 ^a
Fully vaccinated with booster	n (%)	105 (40.5)	181 (78.0)	<0.001 ^a
SARS-CoV-2 IgG antibody level <500 BAU/mL	n (%)	65 (32.7)	125 (53.9)	<0.001 ^a
At presentation				
Symptomatic infection	n (%)	202 (78.0)	226 (97.4)	<0.001 ^a
Haemoglobin (g/dL)	mean ± SD	10.6 ± 1.70	13.5 ± 15.4	0.005 ^a
White cell count (x10 ⁹ /L)	mean ± SD	6.96 ± 3.03	6.63 ± 2.23	0.167
Platelet count (x10 ⁹ /L)	mean ± SD	194 ± 4.56	210 ± 67.1	0.008 ^a
C-reactive protein (mg/L)	mean ± SD	39.8 ± 3.02	21.0 ± 32.2	<0.001 ^a
Albumin (g/L)	mean ± SD	34.3 ± 4.92	37.8 ± 6.28	<0.001 ^a
Consolidation on X-ray	n (%)	56 (24.5)	25 (10.8)	<0.001 ^a
Treatment				
Monoclonal antibody	n (%)	34 (13.1)	118 (50.9)	<0.001 ^a
Remdesivir	n (%)	157 (60.6)	109 (47.0)	0.003 ^a
Dexamethasone	n (%)	45 (17.4)	11 (4.7)	<0.001 ^a
Tocilizumab	n (%)	1 (0.4)	2 (0.9)	0.605
Outcomes				OR (95% CI), P value
Mortality - all	n (%)	13/259 (5.0)	1/232 (0.4)	0.082 (0.011–0.631), 0.002 ^a
- delta (n=117)	n (%)	6/91 (6.6)	0/26 (0)	0.248 (0.014–4.55), 0.034
- omicron (n=374)	n (%)	7/168 (4.2)	1/206 (0.5)	0.112 (0.014–0.921), 0.025 ^a
Ventilation - all	n (%)	12/259 (4.6)	3/232 (1.3)	0.271 (0.075–0.972), 0.037 ^a
- delta (n=117)	n (%)	4/91 (4.4)	2/26 (7.7)	1.813 (0.313–10.5), 0.613
- omicron (n=374)	n (%)	8/168 (4.8)	1/206 (0.5)	0.098 (0.012–0.788), 0.013 ^a
Oxygen requirement	n (%)	56 (21.6)	11 (4.7)	5.54 (2.83–10.9), <0.001 ^a
4C score	mean ± SD	9.56 ± 2.60	4.95 ± 3.01	P<0.001 ^a

CI: confidence interval; OR: odds ratio; SD: standard deviation

^a Statistically significant variables.

95% CI 1.05–1.24, $P=0.003$), higher white cell count (per 1mg/dL increase, OR 1.51, 95% CI 1.24–1.83, $P<0.001$), higher C-reactive protein (per 1g/L increase, OR 1.01, 95% CI 1.002–1.023, $P=0.020$), and lower serum albumin (per 1g/L decrease, OR 1.15, 95% CI 1.02–1.30, $P=0.024$). The type of renal replacement therapy was not significant on multivariate analysis.

COVID-19 therapeutics employed in this cohort included remdesivir (54.2% of all patients), monoclonal antibodies (31.0%), dexamethasone (11.4%), and tocilizumab (0.6%). Transplant recipients were more likely than dialysis patients to receive monoclonal antibodies (50.9% vs 13.1%, $P<0.001$), but less likely to receive remdesivir (47.0% vs 60.6%, $P=0.003$). Mortality was higher in patients receiving remdesivir (OR 11.5, 95% CI 1.49–88.7, $P=0.002$) or dexamethasone (OR 35.2, 95% CI 9.47–131, $P<0.001$). There was no association between receipt of monoclonal antibodies and mortality.

Our audit identified a mortality of 2.9% and a mechanical ventilation rate of 3.1% among COVID-19 patients on renal replacement therapy, which compares favourably with international case fatality rates in ESKD cohorts, but is significantly higher than the overall case fatality rate in Singapore of 0.07%.⁶ Older age, leukocytosis, elevated C-reactive protein, or hypoalbuminaemia on admission should alert clinicians to an elevated risk of COVID-19 mortality. While COVID-19 vaccination and SARS-CoV-2 antibody levels were protective in prior literature,^{7,8} these were not associated with reduced mortality in our audit, which may be due to inadequate statistical power. Contrary to popular belief, transplant recipients had lower mortality than patients on dialysis (although non-significant on multivariate analysis), despite immunosuppression. This may be due to a selection of fitter patients (as reflected in a lower Charlson comorbidity index) for transplantation, higher uptake of COVID-19 vaccination in transplant patients, and better ability to self-isolate. Hence, a potential consideration in planning for future pandemics may be modifying dialysis centre infrastructure to enable isolation of patients from each other, and empowering dialysis centres to vaccinate patients on-site.

Significant differences in treatment strategy between transplant recipients and dialysis patients were noted. Transplant recipients may have been more likely to be offered oral monoclonal antibodies in accordance with a previously published hospital-at-home model for COVID-19 infected transplant recipients.^{9,10} The higher mortality observed in

patients receiving remdesivir or dexamethasone may reflect a selection of patients with severe disease. From retrospective audit data, it is difficult to distinguish whether varying treatment strategies contributed to differences in outcomes, or if treatment choices reflected differing disease severity, and this is an important limitation of our study.

Finally, our audit is limited by the inclusion of only patients managed in tertiary care, and may not reflect outcomes among COVID-19 patients managed in primary care or at outpatient dialysis centres. Transplant recipients generally have tight links to their transplant coordinators and may be more likely to present to tertiary care.

Acknowledgements

We wish to acknowledge the following clinicians who contributed greatly to inpatient care of COVID-19 patients: Dr Ho Quan Yao, Dr Htay Htay, Dr Liew Ian Tatt, Dr Liu Peiyun, Dr Michelle Tan Woei Jen, Dr Phang Chee Chin, and Dr Sobhana D/O Thanagaraju.

Keywords: COVID-19, delta, dialysis, nephrology, omicron, transplant

REFERENCES

1. Jager KJ, Kramer A, Chesnaye NC, et al. Results from the ERA-EDTA registry indicate a high mortality due to covid-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int* 2020;98:1540-8.
2. Torres R, Toro L, Sanhueza ME, et al. Clinical Efficacy of SARS-CoV-2 vaccination in hemodialysis patients. *Kidney Int Rep* 2022;7:2176-85.
3. Quiroga, B, Ortiz A, Cabezas-Reina CJ, et al. Evolving spectrum but persistent high mortality of COVID-19 among patients on kidney replacement therapy in the vaccine era: the Spanish COVID-19 KRT Registry. *Clin Kidney J* 2022;15:1685-97.
4. Tylicki, L, Biedunkiewicz B, Puchalska-Reglińska E, et al. COVID-19 vaccination reduces mortality in patients on maintenance hemodialysis. *Front Med (Lausanne)* 2022; 9:937167.
5. Ministry of Health, Singapore. Two imported covid-19 cases tested preliminary positive for omicron variant, December 2021. Updated 2 December 2021. <https://www.moh.gov.sg/news-highlights/details/two-imported-covid-19-cases-tested-preliminarily-positive-for-omicron-variant>. Accessed 1 June 2023.
6. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/region/wpro/country/sg>. Accessed 1 June 2023.
7. Sibbel, S, McKeon K, Luo J, et al. Real-world effectiveness and immunogenicity of bnt162b2 and mrna-1273 sars-cov-2 vaccines in patients on hemodialysis. *J Am Soc Nephrol* 2022; 33:49-57.
8. Montez-Rath ME, Garcia P, Han J, et al. SARS-CoV-2 infection during the omicron surge among patients receiving dialysis: the role of circulating receptor-binding domain antibodies and vaccine doses. *J Am Soc Nephrol* 2022;33:1832-9.

9. Liew IT, Tan WJM, Ho QY, et al. An outpatient model of care for covid-19 infected kidney transplant patients - the hospital-at-home. *Nephrology (Carlton)* 2023;28:283-91.
10. Liew IT, Tan WJM, Ho QY, et al. COVID-19 infected kidney transplant patients outpatient management—a single-center experience with a hospital-at-home program. *Transplantation* 2022;106:e525-7.

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