ORIGINAL ARTICLE

# From Alpha to Omicron: anatomy of the SARS-CoV-2 pandemic in an outpatient haemodialysis unit in Johannesburg, South Africa

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## ABSTRACT

**Background:** Recipients of kidney replacement therapy are more susceptible to severe disease and mortality from SARS-CoV-2 infection compared to the general population. We evaluated disease kinetics and clinical outcomes across four COVID-19 outbreak waves in the haemodialysis unit of a tertiary-level hospital in South Africa.

**Methods:** Data from 70 patients were analysed. Temporal trends in SARS-CoV-2 infection, as diagnosed by nasopharyngeal RT-PCR swab, were described as were the severity of resultant COVID-19 disease, survival outcomes, and recurrent infections. The effect of patient-related demographic and comorbidity factors, and that of probable SARS-CoV-2 variants on disease severity and recurrence, were also assessed.

**Results:** Three-quarters of patients in this unit ultimately developed SARS-CoV-2 infection. The majority of infections were asymptomatic or of mild clinical presentation. The Alpha variant (the first) wave and the Delta variant (the third) wave accounted for most infections. COVID-19 disease was more frequently severe in the Delta variant wave and all mortalities in this cohort occurred in this phase. Comorbid diabetes was associated with severe disease. The duration of swab positivity was longer following clinically severe infection. Prior episodes of SARS-CoV-2 infection reduced clinical severity at subsequent re-infection and shortened the period of swab positivity.

**Conclusion:** This study presents the first description of the COVID-19 pandemic in an African haemodialysis unit. Significant temporal differences in infection rates, disease severity, and survival outcomes were demonstrated over the course of the pandemic in this vulnerable population. Evolving SARS-CoV-2 virulence and patient immunity potentially accounts for these differences.

**Keywords:** COVID-19, variants of concern, haemodialysis, outcomes.

## INTRODUCTION

In-centre haemodialysis is associated with an increased risk of acquiring infection with the novel Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) through healthcare-associated transmission of the virus [1]. Prolonged viral shedding in patients living with kidney failure (KF) may compound the risk of infection through patient-to-patient transmission [2,3].

Coronavirus disease 2019 (COVID-19) severity has been reported to be increased in patients living with advanced chronic kidney disease both locally and elsewhere [4,5]. The case fatality rate in patients receiving chronic dialysis in the developed world has been documented to be significantly higher than that of the general population [6], approaching 30% in some series [7]. Comorbidities such as ischaemic heart disease, diabetes mellitus, and hypertension, as well as the advanced age of the dialysis population in these series are likely contributors to the excess mortality in these reports [1].

Mortality risk is also affected by virological factors. Since the onset of the COVID-19 pandemic in March 2020, global phylogenetic surveillance has identified multiple SARS-CoV-2 variants of concern (VOC) as key pathogenic drivers of recurrent widespread outbreaks of

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COVID-19 disease [8]. Differences in the transmissibility and virulence of the dominant VOC in each pandemic wave [9] determine the number of patients infected and the clinical severity of subsequent COVID-19 disease, in turn contributing to risk of death. Local data indicate higher rates of infection and more frequent clinically severe disease with concomitantly higher case fatality rates in the general population during the Beta and Delta waves of the pandemic (B.1.351 and B.1.617.2 variants of concern, respectively) [10].

Disease severity and mortality rates in patients receiving kidney replacement therapy (KRT) who acquire SARS-CoV-2 infection remain underreported in the African context. Emerging data from developed countries suggest that patients of African descent living with KF have milder COVID-19 disease and are at lower risk for SARS-CoV-2 infection-related mortality [7,11,12]. In South Africa, 53% of KRT recipients are of Black African ethnicity; application of transplant eligibility as an entrance criterion for the state-funded dialysis programme in this country selects for a younger population with fewer comorbidities [13]. In comparison, dialysis populations in high-income countries demonstrate a White race predominance and are older with higher rates of comorbidity [14]. It is therefore possible that the mortality risk of SARS-CoV-2 infection in dialysis patients reported in the international literature may not be representative of the African context.

This study retrospectively describes the epidemiology and disease kinetics of multiple outbreaks of SARS-CoV-2 as experienced in an urban state-sponsored dialysis programme in Johannesburg, South Africa. In characterising disease severity and outcomes in relation to different variants, potential prognosticating factors have been identified which may contribute to future pandemic preparedness in this high-risk patient group.

## METHODS

A retrospective review was conducted of clinical records of patients attending the chronic haemodialysis (HD) unit at Helen Joseph Hospital (HJH), a tertiary-level facility that services a demographically diverse, lower-income population residing in the western areas of Johannesburg. Positive cases of SARS-CoV-2 were identified from a clinical database employed to facilitate isolation protocols in the centre. Anonymised data were extracted and stored in a password-protected Excel study data set, which was subsequently exported for analysis using STATA version 17.0 (StataCorp LLC, College Station, TX, USA).

Per in-centre protocol, all cases of SARS-CoV-2 included in this study were diagnosed on nasopharyngeal swab using reverse transcriptase polymerase chain reaction (RT-PCR). Positive patients isolated on a designated COVID-19 dialysis shift received a weekly RT-PCR swab. The duration of swab positivity in this study therefore reflects the number of days until a negative swab permitted de-isolation. The severity of COVID-19 disease was determined using contemporaneous clinical records as severe (requiring intensive care unit admission for ventilatory support or death due to COVID-19), moderate (requiring general ward admission for supplementary oxygen), mild (symptomatic cases not requiring supplemental oxygen that were managed on an outpatient basis), or asymptomatic (RT-PCR swab positive during surveillance following known exposure or in preparation for elective surgery with no documented symptoms).

Only those patients already accepted for long-term HD at the time of diagnosis of the first case of SARS-CoV-2 in this unit (15 May 2020) were included in this study. Dialysis vintage as analysed reflects the number of years on dialysis at the start of the SARS-CoV-2 outbreak in this setting. To accommodate month-to-month dialysis prescriptions in this unit, estimated dry weight as analysed reflects the averaged value of this parameter for an individual patient over the course of the study. For the purposes of analysis, "cardiovascular disease" was defined as a known diagnosis of ischaemic heart disease or cardiomyopathy from other causes with reduced ejection fraction.

COVID-19 waves were defined as per the National Institute for Communicable Diseases (NICD) [15]. In the absence of access to genotype testing at HJH, the dominant VOC in each SARS-CoV-2 wave as identified by the NICD was used as an indicator of the probable aetiological variant driving periods of increased transmission in the HD unit. Numbers of cases, COVID-19 disease severity, and outcomes in terms of deaths directly attributable to COVID-19 and duration of swab positivity in survivors were described for each wave. Predictors of COVID-19 disease severity were modelled using logistic regression. Linear regression modelling was used to evaluate the effect of parameters on the duration of swab positivity. Categorical variables were analysed between waves, disease severity clinical groups, and recurrent infection categories using the Fisher exact or Pearson chi-squared tests as appropriate. The Mann–Whitney U test was used for continuous variables.

Permission for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (reference number M220203).

## RESULTS

Seventy outpatients were receiving long-term haemodialysis in this unit during the course of the SARS-CoV-2 outbreak in South Africa (Table 1).

A total of 63 cases of SARS-CoV-2 were diagnosed in 53 patients (76% of the outpatient haemodialysis unit) during the course of the study (Table 2). The first documented case was diagnosed on 15 May 2020 and the final patient recovered from presumed Omicron B.1.1.529 variant infection on 8 January 2022 (Figure 1). The third, Delta (B.1.617.2 variant) wave contributed the largest number of infections (n = 24), followed by the first, Alpha (Asp614Gly variant) wave (n = 21).

**Table 1.** Baseline characteristics of all outpatients receiving haemodialysis at HJH (n=70).

| | |
|---|---|
| Age (years) | 43.8 [35.7–51.0][a] |
| Dialysis vintage (years) | 4 [2.6–7.0][a] |
| Dry weight (kg) | 65.8 [57.5–74.5][a] |
| Female sex | 36 (51)[b] |
| HIV positive status | 15 (21)[b] |
| Comorbid diabetes | 10 (14)[b] |
| Comorbid hypertension | 67 (96)[b] |
| Comorbid cardiovascular disease | 9 (13)[b] |
| Comorbid connective tissue disease[c] | 5 (7)[b] |
| Comorbid chronic respiratory disease[d] | 1 (1)[b] |

[a]Values are expressed as median [interquartile range].
[b]Values are expressed as number (percentage of total).
[c]Includes 4 patients known with systemic lupus erythematosus and 1 patient with diffuse scleroderma.
[d]Includes a patient living with diffuse scleroderma with restrictive lung disease.

COVID-19 disease severity varied between waves. The third, Delta wave was associated with more frequent severe infection; in contrast, the first, Alpha wave and the fourth, Omicron wave were associated with greater frequencies of asymptomatic infections (P = 0.003). Although no association was shown with graduated increasing clinical severity, premorbid diagnosis of diabetes was independently associated with risk of severe disease category. Age, averaged dry weight, comorbid cardiovascular disease, and positive HIV infection status did not appear to affect the severity of COVID-19 disease in this series (Table 3).

Six patients died of COVID-19 during the course of this study, equating to a case fatality rate for this unit of 9.5%. All deaths attributable to COVID-19 in this series occurred during the third, Delta (B.1.617.2 variant) wave; the association of the Delta variant with adverse survival outcomes was statistically significant (P = 0.002). Characteristics of the six mortalities in this series are shown in Table 4.

The median time to negative swab in survivors was 28 days (interquartile range 15–39 days). The duration of RT-PCR nasopharyngeal swab positivity appeared to decrease during the course of the pandemic, from greater than 30 days for the first and second waves to 13 days for the fourth wave (P = 0.004, Figure 1). Swab positivity was of longer duration in those patients with more severe COVID-19 disease (34.5 days in patients with moderate to severe disease compared to 21.5 days in those with mild or asymptomatic presentation, P = 0.011). Reflecting these findings, multivariate linear regression analysis found increased duration of swab positivity in association with a more severe clinical disease category, and shorter duration of swab positivity in association with successive wave outbreaks (Table 5).

**Table 2.** Summary of COVID-19 disease kinetics across outbreak waves.

| | Alpha wave | Beta wave | Delta wave | Omicron wave | Total |
|---|---|---|---|---|---|
| VOC | Asp614Gly | B.1.351 | B.1.617.2 | B.1.1.529 | |
| Number of cases | 21 | 7 | 24 | 11 | 63 |
| Severity[a] | | | | | |
| Asymptomatic | 12 (57) | 2 (29) | 9 (28) | 9 (81) | 32 (51) |
| Mild | 5 (24) | 2 (29) | 3 (13) | 2 (18) | 12 (19) |
| Moderate | 4 (19) | 3 (43) | 3 (13) | 0 | 10 (16) |
| Severe | 0 | 0 | 9 (38) | 0 | 9 (14) |
| Recoveries | 21 | 7 | 18 | 11 | 57 |
| Duration swab positive (days)[b] | 32 [23–43] | 35 [20–62] | 23 [14–34] | 13 [7–15] | 28 [15–39] |
| Deaths | 0 | 0 | 6 | 0 | 6 |

[a]Values are expressed as number (percentage of total).
[b]Values are expressed as median [interquartile range.]

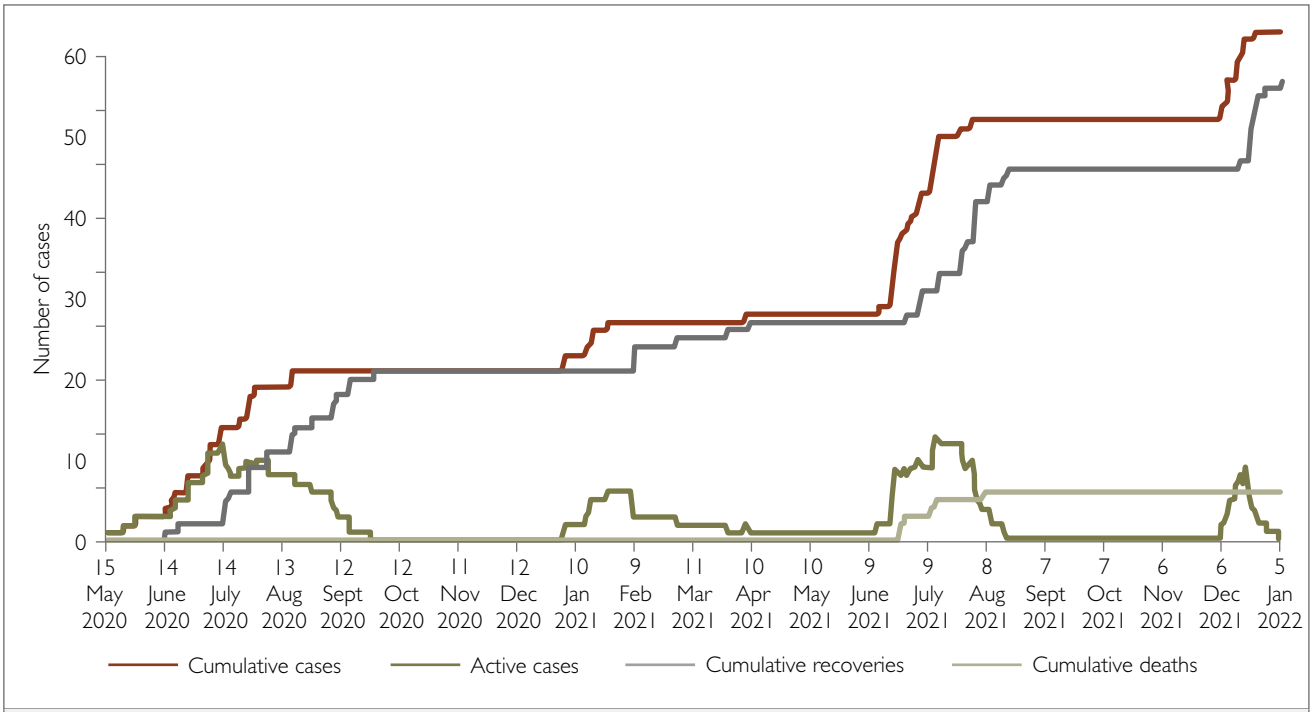


**Figure 1.** Timeline of SARS-CoV-2 infections at HJH over the course of the COVID-19 pandemic (15 May 2020–8 January 2022).

**Table 3.** Predictors of severe disease.

| Predictor variables | Reference category | Odds ratio (95% CI) | P |
|---|---|---|---|
| Age (years) | – | 1.01 (0.93–1.09) | 0.878 |
| Averaged dry weight (kg) | | 0.95 (0.88–1.03) | 0.194 |
| Male sex | Female sex | 3.28 (0.50–21.32) | 0.214 |
| HIV positive | HIV negative | 0.83 (0.12–5.68) | 0.851 |
| Diabetes mellitus | Non-diabetic | 6.70 (1.18–44.42) | 0.033 |
| Cardiovascular disease | No CVS disease | 0.73 (0.06–8.16) | 0.802 |
| Previous SARS-CoV-2 infection | No previous SARS-CoV-2 infection | 0.38 (0.03–4.58) | 0.447 |

*All severe disease episodes were diagnosed during the third, Delta wave.

**Table 4.** Characteristics of mortalities due to COVID-19.

| Case number | Age (years) | Gender | Dialysis vintage (years) | Averaged dry weight (kg) | BMI (kg/m²) | Diabetes | Hypertension | Cardiovascular disease | HIV status | Preceding SARS-CoV-2 infection | Vaccinated |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 46.1 | Female | 1 | 49 | 20.7 | No | Yes | No | Negative | No | Yes |
| 2 | 43.5 | Female | 3 | 50 | 23.4 | Yes | Yes | No | Positive | No | No |
| 3 | 39.9 | Male | 5 | 72 | 21.1 | No | Yes | No | Negative | No | Yes |
| 4 | 26.6 | Male | 2 | 68 | 17.3 | No | Yes | No | Negative | No | No |
| 5 | 55.5 | Male | 9 | 67 | NA[a] | Yes | Yes | No | Positive | No | NA[a] |
| 6 | 33.5 | Male | 2 | 59 | 19.7 | No | Yes | No | Negative | No | No |

[a]NA = not retrospectively available.

**Table 5.** Factors affecting duration of RT-PCR swab positivity in survivors.

| Predictor variables | Reference category | β (95% CI) | P |
|---|---|---|---|
| Age (years) | – | 0.10 (-0.37 to 0.56) | 0.678 |
| Male sex | Female sex | -1.42 (-11.59 to 8.75) | 0.780 |
| HIV positive | HIV negative | 7.03 (-5.15 to 19.22) | 0.251 |
| Diabetes mellitus | Non-diabetic | 5.77 (-6.42 to 17.97) | 0.345 |
| Successive SARS-CoV-2 wave | - | -7.01 (-11.61 to -2.41) | 0.004 |
| SARS-CoV-2 disease category | Asymptomatic | 7.72 (2.85 to 12.59) | 0.003 |

Recurrent infections with SARS-CoV-2 occurred in 10 patients at a median of 341 days after index diagnosis (interquartile range 175–382 days). Seven patients experienced a recurrence of infection during the third Delta (B.1.617.2 variant) wave; three recurrent infections were diagnosed during the fourth Omicron (B.1.1.529 variant) wave. Median duration of swab positivity during index diagnosis was longer in those patients who subsequently developed re-infection (42 days versus 30 days in those with a single episode, P = 0.016). Higher rates of recurrence were observed for those patients with initial infection during the second, Beta (B.1.351 variant) wave (50%, compared to 29% of patients in the first and 6% of patients in the third waves, P = 0.048). There were no deaths of those patients with recurrent SARS-CoV-2 infection and recurrent infections were for the most part asymptomatic (n = 7) or mild (n = 2), although one patient experienced a severe bout of COVID-19 upon re-infection. The median duration of swab positivity in recurrent infections was 15 days, significantly shorter than that of index diagnoses at 32 days (P = 0.016).

## DISCUSSION

This is the first report from Africa offering insights into temporal trends in SARS-CoV-2 infections and their clinical outcomes in an urban haemodialysis unit during the course of the pandemic. The principal findings of the study include the identification of male gender and comorbid diabetes as risk factors for more severe COVID-19 disease in this population. Clinical outcomes were poor in the Delta variant wave during which all mortalities in this cohort occurred; the case fatality rate of 9.5% in this series was, however, lower than that reported previously [3]. Despite the application of a *sui generis* in-centre protocol which emphasised isolation of all known or suspected SARS-CoV-2 infection cases as well as those with a history of positive contact with the virus (described in [3]), three-quarters of our patients were eventually RT-PCR positive for the virus. The majority of infections in this cohort were asymptomatic or clinically mild. Serial RT-PCR swab demonstrated prolonged positivity among survivors, which may indicate the importance of swab-directed isolation protocols in limiting in-centre transmission.

The proportion of patients with documented SARS-CoV-2 infection in the study population (76%) closely parallels sero-epidemiological data from the local context. Surveys of the communities served by HJH indicate anti-spike or anti-nucleocapsid IgG seroprevalence rates of 77–80% [16]. Vaccination rates in these communities are low [16], and it is probable that most of these seropositive cases represent antecedent infection. Outbreak patterns in this cohort additionally show homology with those reported for Gauteng province, with the Delta wave contributing the highest number of infections, followed in descending order by the Alpha, Omicron, and Beta waves [16]. Lack of pre-existing immunity to the novel SARS-CoV-2 virus and viral spike protein mutations which enhanced transmissibility in the Alpha and Delta waves, respectively, account for these patterns [17]. The proportional severity of COVID-19 disease across outbreak waves in this series broadly conforms to those reported for Gauteng and for South Africa as a whole, with a greater proportion of severe cases recorded during the Delta and Beta waves [10,16].

The majority (51%) of SARS-CoV-2 infections in this study group were asymptomatic. The true incidence of asymptomatic infection in the general population has been difficult to determine but may account for between 8% and 39% of cases [18]; younger patients may be more likely to be asymptomatic carriers of infection [19]. Thirty percent of cases in this series required admission for COVID-19 disease, nine of whom (30% of admissions) needed treatment in an intensive care unit. Contemporaneous South African data indicate the incidence rates of moderate to severe COVID-19 disease (that is, cases requiring hospital admission) of between 8% and 13%, with severe cases accounting for 34% to 63% of hospitalised patients [10].

Taken together, these data suggest lower rates of mildly symptomatic COVID-19 in our dialysis cohort with increased incidence of moderate to severe and asymptomatic disease compared to the general population. KRT entrance criteria in South African state-sponsored programmes in force account for our relatively young and biologically fit HD cohort [13], which may explain the prevalence of asymptomatic infection reported. The higher rates of moderate to severe disease in this group are consistent with the known association of advanced CKD with COVID-19 severity [4,5].

Comorbid diabetes was associated with increased severity of COVID-19 in this cohort. Similar findings have been reported in population-based analyses of COVID-19 disease severity; postulated reasons for the effect of these factors include altered immune response to infection and associated cardiovascular risk [20]. Previous studies in the general and dialysis populations have reported increased disease severity and risk of mortality in males and with increasing age and history of antecedent cardiovascular disease [7,20-22]. The relative absence of older patients in our study population arising from transplant eligibility selection criteria may explain the lack of effect of age on COVID-19 severity in the present study. Interventions to address known cardiovascular disease to maintain transplant eligibility in this population may similarly underlie the lack of effect for this parameter on COVID-19 severity reported in this study. Immunity acquired through SARS-CoV-2 infection is known to ameliorate disease severity in the event of re-infection in haemodialysis patients, as observed in this cohort [23].

The COVID-19 case fatality rate of 9.5% in our dialysis population exceeds that reported for the general South African population (2.5%) [24], but is considerably lower than that documented for dialysis-dependent CKD populations in developed settings (23–31.7%) [7,25]. Patient selection for the HD programme in the unit at HJH, using transplant eligibility criteria, may again account for this observation; European registry data indicate that patients on transplant waiting lists have an 81% lower mortality from COVID-19 than those not fit for transplant [26]. Males were over-represented among mortalities, consistent with known sex bias in risk of death due to COVID-19 [21]. No overt association between mortality and age, averaged dry weight, body mass index, or comorbidity with diabetes, cardiovascular disease or HIV infection was appreciable in this cohort. All mortalities occurred in patients who were hypertensive. Increased risk of mortality from COVID-19 in patients with pre-existing hypertension in the general population may arise from the confounding effects of ageing and cardiovascular comorbidity [27]; the potential effect of hypertension on outcomes in this series is difficult to distinguish from that of advanced chronic kidney disease.

We [3] and others [28] have previously reported prolonged RT-PCR viral shedding in patients living with advanced CKD. It is unclear whether persistent positive swabs after clinical recovery indicate shedding of replication-competent whole virus or merely represent particles of virions lysed by a successful immune response. The apparent effect of COVID-19 disease severity on the duration of swab positivity in this series could be evidence of either possibility – significant viral load resulting in more severe disease may lead to slower clearance of active virus or may presage a large volume of inactive virus particles being shed for a prolonged period. Since prolonged shedding of active virus has been demonstrated in other immunocompromised patient groups [29], it would be reasonable to exercise caution in de-isolating such patients until a negative swab is achieved.

SARS-CoV-2 infection recurred in 10 patients in this series. Antibody titres acquired during SARS-CoV-2 infection decrease significantly after 6 months in patients on HD [23]. We have previously reported on low rates of vaccine uptake in our cohort, with only 30% of patients having been vaccinated at the time of the Omicron outbreak [30]. Absent immune system rechallenges through vaccination, time-dependent decline in circulating neutralising antibody may allow for late re-infection as demonstrated in our cohort. In contrast, induction of cellular immunological memory may provide for a robust anamnestic response in the event of re-infection [31]. Although the longevity of cellular memory against SARS-CoV-2 has yet to be established, prolonged protection may be possible. For example, previous experience with SARS-CoV-1 has demonstrated the induction of persistent memory T cells in survivors of the 2002 SARS outbreak many years after diagnosis [32]. Furthermore, conservation of memory T-cell recognised epitopes by subsequent VOCs ameliorates viral humoral immunological escape [31]. These characteristics of cellular memory are likely to contribute to the reduced disease severity which has been reported in patients experiencing recurrent infection [33].

Duration of viral shedding in survivors reflects severity of COVID-19 disease [34], and both are known to affect the magnitude and longevity of neutralising antibody production [35]. Prolonged viral shedding as indicated by RT-PCR swab positivity during index infection in patients who subsequently developed re-infection is therefore an unexpected finding in this study. Since prolonged shedding may be observed in immunocompromised patients [29], this association may be evidence of immunoparesis in this group,

which may have resulted in weaker humoral immunity and increased probability of re-infection. Further investigation with viral cultures and measurement of neutralising antibodies is necessary to test this hypothesis.

There are some limitations to our study. The single-centre nature of the analysis with a relatively small number of patients limits the generalisability of our findings. In addition, our resource-constrained setting limited access to genotype testing, which prevented validation of the exact variant present in each period of increased transmission. We further acknowledge that qualitative RT-PCR swabs do not differentiate between shedding of inactive viral particles as opposed to active, replication-competent virus. In the absence of facilities for genomic and culture-based testing, we used regular interval swabbing to identify periods of increased transmission in our unit and concluded that a negative RT-PCR swab in a previously positive patient to be an acceptable indication of viral clearance when combined with clinical recovery.

## CONCLUSION

This first African description of the SARS-CoV-2 outbreak in an outpatient haemodialysis unit across multiple variants of concern adds to existing knowledge of the risks posed to this vulnerable population by infection with SARS-CoV-2. Analysis of this data suggests reduced incidence of severe disease and mortality in the local context compared to that reported from the developed world, possibly reflecting transplant eligibility-related dialysis entrance criteria. High rates of infection were nevertheless recorded in this series despite the imposition of strict isolation practices; the significant proportion of asymptomatic infections in this cohort is likely to have contributed to in-centre transmission. Prolonged detection of shed virus in survivors urges caution in de-isolation protocols to ameliorate risk of transmission. Consistent with established risk factors, diabetes and male sex in this series appear to contribute to an increased risk of severe disease or mortality.

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### Conflict of interest

The authors have no conflict of interest to declare.

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