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Prolonged SARS-CoV-2 viral shedding in patients with Chronic Kidney Disease.

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Keywords: CKD, SARS-CoV-2, shedding

Running Title: SARS-CoV-2 viral shedding in patients with CKD
Prolonged SARS-CoV-2 viral shedding in patients with Chronic Kidney Disease.

**ABSTRACT**

Recent World Health Organization guidance has aimed to provide pragmatic guidance acknowledging the role of sequential nasopharyngeal swabs taken >24 hours apart for SARS-CoV-2 in high risk populations. Patients with chronic kidney disease (CKD) are known to have an altered immune milieu which may be associated with a delay in viral clearance.

Here, a cross-sectional observational study of 138 patients admitted with SARS-CoV-2 infection at two large regional hospitals in Scotland, UK examined the median time to two consecutive negative nasopharyngeal swabs for SARS-CoV-2 in an inpatient population. The median time from admission to the first of two consecutive negative nasopharyngeal swabs was 18 days (range = 1-44) in patients with CKD, compared with 11 days (range: 1-71) in patients without CKD (P = 0.0007).
Multivariable linear regression analysis using explanatory variables of age, sex, SARS-CoV-2 disease severity, key comorbidities and renal function showed that declining eGFR was independently associated with prolonged time to viral clearance.

Our data suggest that patients with CKD who are admitted to hospital with SARS-CoV-2 take longer to achieve sequential negative nasopharyngeal swab RT-PCR results than those without CKD. This has implications for renal service provision, discharge planning and hospital capacity as well as a direct impact on patients due to extended hospital stay, anxiety and stigmatisation.

Key Words: SARS-CoV-2, CKD, Viral shedding.
Introduction

Currently, clinical diagnosis of SARS-COV-2 is made primarily using a viral throat swab and subsequent positive PCR result over a pre-specified CT threshold. Initial interim World Health Organization (WHO) guidance recommended confirming clearance of SARS-CoV-2 in clinically recovered patients by demonstrating two negative quantitative reverse transcription PCR (RT-PCR) results on sequential nasopharyngeal swabs taken >24 hours apart. \(^1\) While the link between PCR swab positivity and infectious risk via viral shedding has been questioned,\(^2\) recent WHO guidance has provided pragmatic guidance acknowledging a potential role for sequential negative swabs in high risk populations or where infective risk to others is high.\(^3\)

Immune dysfunction is well-recognized in chronic kidney disease (CKD). Furthermore, patients with CKD may have previously received immunosuppressive therapies, or have additional risk factors such as hypertension that could be associated with a delay in viral clearance. Certainly, persistent of SARS-CoV-2 has been noted in immunosuppressed hosts.\(^4\) A recent review of 79 studies of SARS-CoV-2 found a mean SARS-CoV-2 RNA shedding duration in upper respiratory tract of 17 days but none described patients with CKD.\(^5\) We hypothesized that this altered immune milieu in CKD may lead to delayed clearance of the SARS-CoV-2 virus, prolonged RT-PCR positivity and longer inpatient stay for patients awaiting negative nasopharyngeal swabs. This would have important clinical implications for service
provision, discharge planning and communicating expectations and care pathways with our patients.

**Methods**

This cross-sectional observational study involved patients admitted with SARS-CoV-2 infection at the Queen Elizabeth University Hospital Glasgow and Edinburgh Royal Infirmary, Scotland, UK between 01/03/2020 and 31/05/2020. Exemption from formal ethical review was granted as data were routinely collected during normal clinical care and were aggregated and anonymised. Local data-protection policies and best practice were followed per Caldicott guidance.6

Patients were identified through routinely collected healthcare-data. Patients over the age of 18 years were eligible for inclusion if admitted from 01/03/2020 to 31/05/2020 and had a positive viral swab for SARS-CoV-2 within 48 hours of admission. All patients who remained in hospital until two consecutive negative swabs were obtained prior to discharge were included. Swabs were tested at most every 48 hours once free from symptoms as per local protocol.

These are typically patients in nursing homes, residential care homes, or deemed to be an infective risk on discharge to vulnerable individuals.

Patients requiring admission to intensive care unit or high dependency unit were excluded (leaving only level 0 and level 1 patients whose entire admission was spent on medical wards). Patients who did not survive to discharge were excluded. Patients
with acute kidney injury, or who required new renal replacement therapy were
excluded as were renal transplant recipients and kidney donors.

Patients with CKD were identified and stratified according to KDIGO CKD stage based
on MDRD eGFR. Each patient’s acute and historical renal function was reviewed by a
nephrologist. Patient’s electronic health records were consulted in ambiguous cases
to understand the context of any historical eGFR measurements. The first eGFR
considered was the admission eGFR during the SARS-CoV-2 infection. If the eGFR
was >60 ml/min/1.73m² and remained so over the admission (i.e. no AKI) this patient
was considered not to have CKD. Where an eGFR was 60 ml/min/1.73m² or less, we
reviewed all of their available eGFR on that admission to confirm whether the value
was rapidly changing and representing AKI. Next, historical eGFR values were
considered. When more than one value was available these were considered in the
broader clinical context of the patient. For example, if they were consistent with each
other over time, this was felt to be stable CKD. If progressive decline was noted and
the admission eGFR was consistent with the trajectory, we assigned CKD according to
the most recent value.

For the categorical classification of CKD, stages 1 and 2 (eGFR>60) were considered
“no CKD” as per KDIGO.

SARS-CoV-2 infection severity scores were recorded as mild, moderate, severe or
critical as per definitions proposed by Qiu et al. Comorbidities were recorded
including cardiovascular disease, hypertension, diabetes, cancer and HIV status.
The primary outcome was time in days from admission to reach the first of two consecutive negative nasopharyngeal swabs for SARS-CoV-2 infection. SARS-CoV-2 positivity was established using a number of platforms in routine clinical use using RT-PCR assays to detect the RdRP gene and N gene, the E gene or the ORF1a/b and E gene. Multiple platforms allowed for internal re-testing and cross validation in the case of uncertain results.

Difference between groups was tested using the Mann-Whitney test, and a p-value ≤ 0.05 was considered statistically significant. Comparisons between CKD stages were performed with Kruskal-Wallis Rank Sum Test and pairwise Wilcox test using the Holm correction for multiple hypothesis testing. Comparisons of proportions (e.g. comparing sex between CKD status) was performed using a Pearson’s chi-squared test. Multivariable linear regression was performed using the finalfit package. Multivariable linear regression analysis was conducted using the explanatory variables of age, sex, disease severity, comorbidities including cardiovascular disease, hypertension, diabetes, cancer and either the presence of CKD, CKD stage or eGFR. All statistical analyses were performed using R version 4.
Results

138 patients were admitted with SARS-CoV-2 infection and met inclusion criteria. 80 (58%) patients had CKD. The mean age overall was 73 years (SD = 14). Patients with CKD were older with mean age of 76.3 (SD=11.9) as compared to patients without, who had a mean age of 69.1 (SD=16, P=0.008). Patient characteristics are shown in table 1. Overall, 71 (51%) patients were female, although there were a higher proportion of female patients in the CKD group (37% female in group without CKD vs 61% female in group with CKD, P=0.014). Patients with CKD were more likely to have hypertension, cardiovascular disease and have mild SARS-CoV-2 infection. Notably no patients had HIV infection. The mean weekly swabs were 2.31 (range: 0.2 - 4.2) in the control group and 2.15 (range: 0.5 - 4.2) in the CKD group (P=0.58).

The median time from admission to the first of two consecutive negative nasopharyngeal swabs was 18 days (range = 1-44) in patients with CKD, compared with 11 days (range: 1-71) in patients without CKD (P = 0.001) (figure 1a).

CKD, CKD stage or eGFR were independently associated with prolonged time to viral clearance, whereas all other variables were not (figure 1b, table 2). For every decrement in eGFR of 10 ml/min/1.73 m², time to clearance increased by approximately 1 day, accounting for 2.5% of the variation in time to clearance in the data.
Discussion

Our data suggest that patients with CKD who are admitted to hospital with SARS-CoV-2 take longer to achieve sequential negative nasopharyngeal swab RT-PCR results than those without CKD.

Early data suggested viral shedding lasted until approximately 20-31 days after symptom onset.\textsuperscript{10–12} Unfortunately, there were few patients with CKD in these cohorts. However, in 10 renal transplant recipients in Wuhan, viral shedding was indeed longer than a control group (28.4 ± 9.3 vs 12.2 ± 4.6 days).\textsuperscript{12} Of course, these patients are exogenously immunosuppressed and unlikely to be representative of the CKD cohort more broadly. Factors previously associated with prolonged viral shedding in cohorts without CKD were male sex, increased age, hypertension, delayed admission, severe illness, mechanical ventilation and corticosteroid treatment.\textsuperscript{13} Interestingly, despite higher rates of hypertension and cardiovascular disease in patients with CKD, these were not associated with longer time to clearance in our dataset, suggesting that CKD may supersede them as risk factors for delayed clearance when included in analysis, or that these factors are less important when critically ill mechanically ventilated patients are excluded. An understanding length of duration of viral shedding, as it relates to disease severity, is lacking. A recent meta-analysis found 13/20 studies which had recorded disease severity found increased shedding with more severe disease, but the remain studies found either no change or reduced duration.\textsuperscript{5} It is important to note that
the presence of RT-PCR positivity on nasopharyngeal swab does not imply infectivity but does have a significant impact on clinical pathways and length of stay when negative swabs are required prior to discharge. Sequential negative tests nonetheless remain a tool in clinical decision making and risk assessment.

There are important limitations to note. There is potential for lead time bias if patients with CKD present earlier to hospital, although this would have resulted in an apparent decrease in time to clearance. We have no record of the duration of acute illness – a longer duration of symptomatic illness in patients with CKD could delay viral clearance or testing. Our control group was likely to have a similar disease severity as all patients were sick enough to require admission, but remained on medical wards and survived to discharge, as well as sharing the requirement to remain in hospital awaiting negative tests suggesting similar social situations and a minimum shared level of frailty. As discussed in the methods, the sickest of patients were excluded to avoid severe disease confounding results. However, the data did not allow for matching for disease severity, multimorbidity, or associated risk factors that may have contributed to CKD which may have independently contributed to delayed viral clearance, such as hypertension. This is an important when considering the mechanism of our findings. While the pragmatic interpretation of results would remain unchanged – that is, CKD is associated with longer delays to negative swabs, confounders of this nature would alter the underlying pathophysiological explanation. It may not be CKD per se that results in the additional delay.

Nonetheless, the label of CKD captures these risk factors on the wards and we hope
will prompt more in-depth research in future to identify specific mechanisms. The prevalence of CKD is high at 9.1% of the global population.\textsuperscript{14} As such, any delay to viral clearance in such a major cohort, regardless of underlying aetiology, has important implications for patients and clinicians caring for them.

In conclusion, our findings suggest a prolonged time to viral clearance in patients with CKD, with implications for renal service provision, discharge planning and hospital capacity as well as a direct impact on patients due to extended hospital stay, potential anxiety and stigmatisation.
**Acknowledgements:** We thank Sophie McCall Msc, for data extraction at NHS Lothian. No additional compensation was received beyond salary.


7. Li T-Z, Cao Z-H, Chen Y, et al. Duration of SARS-CoV-2 RNA shedding and

Title figure 1. Increased time to SARS-CoV-2 clearance in patients with CKD.

Legend figure 1. A) Days until clearance defined as time from first positive nasopharyngeal swab until first consecutive negative swab. n=138, Mann-Whitney test used for statistical significance testing. B) Coefficient of variability following multivariate regression -0.12 (-0.21 to -0.03, p=0.009). Days until clearance defined as time from first positive nasopharyngeal swab until first consecutive negative swab.
<table>
<thead>
<tr>
<th></th>
<th>NO CKD (N=58)</th>
<th>CKD (N=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
<td>mean (SD)</td>
<td>69.1 (16.0)</td>
<td>76.3 (11.8)</td>
</tr>
<tr>
<td><strong>FEMALE SEX</strong></td>
<td>no. (%)</td>
<td>22 (37.9)</td>
<td>48 (60.8)</td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td>mean (SD)</td>
<td>84.4 (15.9)</td>
<td>38.9 (14.3)</td>
</tr>
<tr>
<td><strong>DIABETES</strong></td>
<td>no. (%)</td>
<td>9 (15.5)</td>
<td>24 (30.4)</td>
</tr>
<tr>
<td><strong>HYPERTENSION</strong></td>
<td>no. (%)</td>
<td>18 (31.0)</td>
<td>45 (57.0)</td>
</tr>
<tr>
<td><strong>CANCER</strong></td>
<td>no. (%)</td>
<td>5 (8.6)</td>
<td>15 (19.0)</td>
</tr>
<tr>
<td><strong>SARS-COV2-SEVERITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MILD</td>
<td>no. (%)</td>
<td>8 (13.8)</td>
<td>24 (30.4)</td>
</tr>
<tr>
<td>MOD</td>
<td>no. (%)</td>
<td>5 (8.6)</td>
<td>9 (11.4)</td>
</tr>
<tr>
<td>SEVERE</td>
<td>no. (%)</td>
<td>45 (77.6)</td>
<td>46 (58.2)</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>no. (%)</td>
<td>20 (34.5)</td>
<td>50 (63.3)</td>
</tr>
</tbody>
</table>

**Table 1 Title**

Patient characteristics

**Table 1 legend:** SD = standard deviation, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate (mL/min/1.73m²)
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DAYS (SD)</th>
<th>COEFFICIENT (MULTIVARIABLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE [1.0,49.0]</td>
<td>17.8 (12.8)</td>
<td>-0.01 (-0.21 to 0.20, p=0.937)</td>
</tr>
<tr>
<td>SEX f</td>
<td>18.9 (13.5)</td>
<td>-</td>
</tr>
<tr>
<td>m</td>
<td>16.6 (12.0)</td>
<td>0.03 (-4.74 to 4.79, p=0.991)</td>
</tr>
<tr>
<td>EGFR [6.0,132.0]</td>
<td>17.8 (12.8)</td>
<td>-0.11 (-0.21 to -0.01, p=0.028)</td>
</tr>
<tr>
<td>DM 0</td>
<td>16.8 (12.5)</td>
<td>-</td>
</tr>
<tr>
<td>m 1</td>
<td>20.7 (13.3)</td>
<td>1.14 (-4.66 to 6.93, p=0.698)</td>
</tr>
<tr>
<td>HTN 0</td>
<td>16.9 (12.1)</td>
<td>-</td>
</tr>
<tr>
<td>m 1</td>
<td>18.8 (13.6)</td>
<td>0.66 (-4.13 to 5.45, p=0.785)</td>
</tr>
<tr>
<td>CANCER 0</td>
<td>18.2 (12.5)</td>
<td>-</td>
</tr>
<tr>
<td>m 1</td>
<td>15.4 (14.2)</td>
<td>-4.63 (-11.04 to 1.79, p=0.15)</td>
</tr>
<tr>
<td>SARS-COV2-SEVERITY Mild</td>
<td>19.6 (14.9)</td>
<td>-</td>
</tr>
<tr>
<td>Mod</td>
<td>18.9 (10.9)</td>
<td>-0.20 (-8.65 to 8.26, p=0.964)</td>
</tr>
<tr>
<td>Severe</td>
<td>17.0 (12.3)</td>
<td>-0.21 (-6.33 to 5.90, p=0.945)</td>
</tr>
<tr>
<td>CVD 0</td>
<td>15.8 (12.4)</td>
<td>-</td>
</tr>
<tr>
<td>m 1</td>
<td>19.6 (12.9)</td>
<td>2.22 (-3.24 to 7.69, p=0.421)</td>
</tr>
</tbody>
</table>

**Table 2 Title**

Multivariable regression analysis summary

**Table 1 legend:** SD = standard deviation, DM = diabetes (type 1 or 2), HTN = hypertension, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate (mL/min/1.73m²). Log-likelihood = -504.74, AIC = 1031.5, R-squared = 0.094, Adjusted R-squared = 0.025