Regular RNA screening detects asymptomatic SARS-CoV-2 infection in haemodialysis patients

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INTRODUCTION

Those receiving in-centre haemodialysis are uniquely vulnerable to coronavirus disease 2019 (COVID-19) due to comorbidity and inability to self-isolate, resulting in high rates of infection and mortality [1]. Evidence for dialysis unit transmission [2] highlights the importance of effective case detection in order to protect this population. However, ~17% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are asymptomatic [3] and this may be higher in an elderly dialysis population [4]. US and UK antibody screens have found only 9.2 and 56.6% of seropositive haemodialysis cases that were previously detected by symptom-led reverse transcription polymerase chain reaction (RT-PCR) testing [5, 6].

Asymptomatic infected individuals can transmit SARS-CoV-2 at an estimated 42% of the risk in symptomatic cases [7, 8], therefore screening for asymptomatic SARS-CoV-2 has been proposed or adopted in a range of populations, predominantly to protect others by case isolation [9, 10].

The efficacy of frequent asymptomatic screening has not been established in the dialysis population, or whether end-stage kidney disease influences antibody responses. To address these questions, we briefly report our experience of regular screening for both acute infection and post-infectious antibody response in a haemodialysis population.

METHODS

As of May 2020, asymptomatic SARS-CoV-2 RT-PCR screening was offered fortnightly to every hospital haemodialysis patient in our region, with monthly SARS-CoV-2 immuno-globulin G (IgG) from July 2020. Verbal consent was obtained as part of clinical care.

Viral RNA obtained from nasopharyngeal swabs was detected by RT-PCR predominantly using the Abbott RealTime SARS-CoV-2 Assay (Abbott, Abbott Park, IL, USA). For Altona and Public Health England RNA-dependent RNA polymerase results, comparative standard curves were used to interpolate Abbott cycle numbers (CNs).

SARS-CoV-2 nucleocapsid IgG was quantified using the Abbot Architect Immunoassay. Titre is an index of chemiluminescent light units for the sample relative to a calibrator. A positive threshold was ≥1.4.

RESULTS

Of 490 haemodialysis patients across our region, 388 had both regular RT-PCR viral RNA screening and at least one IgG antibody test and were included in the dataset. A total of 388 patients had a mean of 8 ± 5.4 RT-PCR tests between 1 May and 7 October, equating to testing on average every 19.9 days. Twenty-seven had a positive RT-PCR; of these, 9 (33.3%) had no symptoms at or following the positive test (Table 1).

A total of 21/34 [sensitivity 61.8%, negative predictive value (NPV) 96.4%] patients with a positive IgG result were found at the time of infection by RT-PCR. Of the 13 patients with prior SARS-CoV-2 infection detected by antibody but ‘missed’ by RT-PCR, retrospective review indicated that only 2 (15%) reported or exhibited clinical features consistent with COVID-19 (including fever or chest X-ray changes).

Since the first UK pandemic wave began in March and April, we hypothesize that these patients may have been infected prior to our regular screening programme. Consistent with this, all 13 patients were identified from the first monthly IgG screen in early July, with no additional ‘missed’ patients detected by subsequent IgG screens, despite a continued rate of new PCR-positive cases. From May onwards, the frequency of swab testing did not differ between PCR-positive IgG-positive and PCR-negative IgG-positive cases (1 May to 7 October mean 13.4 ± 4.9 versus 14.2 ± 2.4 tests; P = 0.59 by unpaired two-tailed t-test), but in March and April, prior to asymptomatic screening, PCR-positive IgG-positive patients were more likely to be swabbed than PCR-negative IgG-positive patients (mean 1.0 ± 0.6 versus 0.3 ± 0.07 tests; P = 0.004) (Figure 1A).

A total of 21/27 PCR-confirmed patients subsequently had a detectable IgG response (sensitivity 77.8%, NPV 98.3%). Positive IgG was more likely in symptomatic than
asymptomatic cases (Fisher’s exact \( P = 0.044 \)) (Figure 1B) and was associated with a lower first-positive RT-PCR CN [mean 14.31 versus 27.02; \( P = 0.039 \) by two-way analysis of variance (ANOVA)], but the CN did not distinguish symptomatic from asymptomatic cases (22.80 versus 18.58; \( P = 0.66 \)) (Figure 1C). Although in individuals with more than one positive test the IgG titre declined with time, the likelihood of serological positivity was unrelated to the time from the first positive PCR swab (mean 103.4 versus 109.0 days for positive versus negative IgG; \( P = 0.34 \)) (Figure 1D) and at a cohort level there was no significant relationship between IgG titre and time (Figure 1E).

**DISCUSSION**

Our data show that offering fortnightly SARS-CoV-2 swabbing on haemodialysis finds the majority of cases. Our sensitivity of 61.8% is likely to be an underestimate, skewed by cases prior to screening, although infections could be missed between tests and weekly screening may improve detection. One-third of cases were asymptomatic and would not be identified by symptom-based testing but can still transmit the virus [11]. While we endeavour to minimize the risk of infection to other patients or staff by hand hygiene and personal protective clothing, proactive screening permits additional targeted measures including patient isolation (in our case, cohorting in a dedicated haemodialysis area).

IgG to nucleocapsid protein was detectable in 77.8% of infected patients tested between 16 and 194 days post-infection, similar to non-dialysis cohorts [12]. Seroconversion is more likely in symptomatic cases and with higher viral titres. Our data indicate that this antibody test performs similarly in the dialysis population as it does more generally.

It is not yet known whether seropositivity confers adequate immune protection, and neutralizing antibodies, e.g. against spike protein, may be more clinically important. The negative IgG result in six patients cannot be interpreted alone, as a lack of longer-term immunity and the role of serological screening to predict re-infection risk or vaccine response in this population remains to be established.

Based on our findings, we advocate regular RT-PCR screening of all dialysis patients. This supports local planning and targeted additional infection control measures, including cohorting, although further studies will be needed to confirm that screening reduces transmission risk and unit outbreaks. Further, the data ensure haemodialysis

**Table 1.** In-centre haemodialysis patients with both SARS-CoV-2 RT-PCR and subsequent IgG results between 1 April and 7 October 2020

| Result                        | All RT-PCR negative | \( \geq 1 \) RT-PCR positive |
|-------------------------------|---------------------|-----------------------------|
| All IgG negative              | 348                 | 6                           |
| \( \geq 1 \) IgG               | 13                  | 21                          |

**FIGURE 1:** (A) Number of SARS-CoV-2 RT-PCR tests performed per dialysis patient in two monthly groups for IgG-positive patients by RT-PCR result. Mean and standard error of the mean shown. (B) Symptomatic versus asymptomatic PCR-positive patients by IgG status. (C) CN, calculated from Ct value, for first positive SARS-CoV-2 RT-PCR by symptom and IgG status; data available for 20 patients. (D) Number of days between first positive SARS-CoV-2 RT-PCR and SARS-CoV-2 IgG testing by IgG result. Lines show mean and standard deviation. In patients with one IgG result, each result is presented as a separate data point. (E) SARS-CoV-2 IgG titre against time from first positive RT-PCR to IgG result. In patients with more than one IgG result, each result is presented as a separate data point. Broken line indicates threshold for positive IgG result.
patients are included in the broader epidemiological understanding of the pandemic.

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CONFLICT OF INTEREST STATEMENT
None declared.

DATA AVAILABILITY STATEMENT
Non-identifiable data underlying this article will be shared on reasonable request to the corresponding author.

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