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Impact of Variant of Concern and Vaccination Status on COVID-19 Infection Virological Dynamics in End Stage Kidney Disease Patients Receiving Haemodialysis

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Summary Statement

This observational cohort study examines the virological dynamics of COVID-19 infection in haemodialysis patients, and the impact of vaccination status and variant of concern on SARS-CoV-2 dynamics.

Abstract

Background: It is unclear if variant of concern and vaccination status impact COVID-19 infection virological dynamics in haemodialysis patients and affect de-isolation protocol for dialysis centres.

Method: We performed a retrospective observational cohort study between February 2020 to September 2021, to examine the virological kinetics of vaccinated and unvaccinated haemodialysis patients with polymerase chain reaction (PCR)-confirmed COVID-19 infection of the delta and pre-delta variants.

Results: Of the 38 subjects with PCR-confirmed COVID-19 infection, we found that individuals infected during the delta-variant period had higher viral load at presentation and required longer duration to achieve a negative PCR swab, compared to those infected in the pre-delta variant period. Time to achieve negative PCR swab was longest in unvaccinated individuals infected during delta-variant period. However, vaccinated and unvaccinated individuals achieved high PCR cycle threshold value of ≥ 25 and ≥ 30 at similar timing.

Conclusion: Our study suggests that patients infected during delta-variant period of COVID-19 illness, have higher viral load at presentation and prolonged viral shedding, especially in the unvaccinated cohort. However, prolonged time to negative PCR is likely due to inactive virus shedding, and that conversion to negative PCR may not be a necessary pre-requisite for de-isolation.

Key words

COVID-19, de-isolation, haemodialysis, vaccination, variant of concern, virus shedding

Introduction

End stage kidney disease (ESKD) patients are at risk of more severe COVID-19 infection and increased mortality (1, 2). In-centre haemodialysis patients are at increased risk of acquiring COVID-19 infection, in part due to the obligatory need to share a common space with other patients and healthcare staff within the community dialysis facility for a significant duration at regular, frequent intervals (3). Hence, infection prevention and control policies to prevent transmission of COVID-19 in dialysis centres is critical to prevent dialysis outbreak clusters.

It is important to establish a safe but practical strategy for ending isolation and precautions for COVID-19 haemodialysis patients. Most community dialysis facilities do not have (or have limited) individual rooms for isolation of COVID-19 haemodialysis patients while they are infectious, and as a result, COVID-19 infected patients are frequently hospitalised or be conveyed to dedicated dialysis facilities for isolation. With each wave of infection, it may not be practical to isolate all haemodialysis COVID-19 patients in hospitals or dedicated dialysis facilities until conversion to negative COVID-19 polymerase chain reaction (PCR) test, as hospital isolation and COVID-19 dialysis facilities are limited in capacity (4), and that prolonged shedding of non-infectious virus fragments has been documented in dialysis patients (5). Conversely, premature termination of isolation precautions when patients remain infectious may put other patients and staff sharing the same centre at risk of COVID-19 illness.

In addition to detecting the presence of target nucleic acid, PCR tests are also indicative of the amount of target nucleic acid in the sample through its cycle threshold (Ct) value. Briefly,

Ct is defined as the number of cycles required for the fluorescent signal to cross the detection threshold, and is hence inversely proportional to the amount of target nucleic acid in the sample (the lower the Ct level the greater the amount of target nucleic acid in the sample). There is no universally accepted cut-off value to classify as high Ct value, and pre-analytic (sampling technique, site, day of illness) and analytic (PCR assay type and instrumentation, extraction techniques, inherent run-to-run variability) factors impact Ct values. In our local data, and as corroborated by other investigators, a cut-off value(s) of 25 – 30 and above are associated with the lack of detection of viable virus by culture. (6, 7) A recent report found that all dialysis patients (not on immunosuppressive therapy) have Ct levels above 28 at 14 days from the first positive COVID-19 PCR test and that SARS-CoV-2 kinetics in ESKD patients are similar to those in the general population (8). This suggest a very low likelihood of infectivity and hence contact and droplet isolation procedures can be safely discontinued for COVID-19 positive patients in the dialysis unit as per the general population, without the requirement for conversion to a negative COVID-19 PCR.

However, emerging variants of concerns, especially the delta variant (World Health Organisation classification, also known as variant B.1.617.2) has raised concerns as it is more transmissible, associates with more severe disease and hospitalisation, including in dialysis patients (9). Furthermore, with the rollout of vaccination programmes around the world, it has been confirmed that great majority of patients on haemodialysis had a seroresponse after vaccination, albeit with a lower antibody titre (10, 11). It is, therefore, unknown if the delta variant and/or the vaccination status alters the virological kinetics in haemodialysis patients and questions remain on the optimal de-isolation strategy in these patients.

In this report, we compare the virological kinetics of vaccinated and unvaccinated haemodialysis patients with PCR-confirmed COVID-19 infection, with the aim to determine a safe and practical strategy for termination of isolation and precautions for COVID-19 haemodialysis patients.

Methods

We included all ESKD patients on regular haemodialysis admitted to the National Centre for Infectious Diseases Singapore for COVID-19 illness between February 2020 to September 2021. All COVID-19 diagnosis were confirmed by nasopharyngeal swab or a combined nasal mid-turbinate and throat swab for real-time PCR for SARS-CoV-2 (12). Results detected for the SARS CoV-2 virus were then checked for the Ct values as a surrogate for the viral load. Serial Ct values of all individuals were analysed for the entire duration of hospitalisation. Whole genome sequencing by National Public Health Laboratory is performed for all patients with SARS-CoV-2 detected by PCR and it was confirmed that the predominant strain of virus in Singapore in 2021 was delta variant, while non-delta variant predominated prior to this. Patients were considered vaccinated if the onset of symptoms or first positive PCR is ≥ 14 days following a second dose of BNT162b2 or mRNA-1273 vaccine and partially-vaccinated if the onset of symptoms or first positive PCR is within 14 days following a second dose of BNT162b2 or mRNA-1273 vaccine or had only received the first dose of the vaccine. Clinical and laboratory data were collected from electronic medical records using a standardised data-collection form. All tests, including PCR, were performed as part of routine care. Repeat PCR swabs were performed at clinician's discretion. However given that prevailing policy was for patients to have negative PCR (till September 21, 2021) or PCR Ct values ≥ 30 (from September

21, 2021 to time of publication) prior to discharge back to dialysis centers, clinical teams tended to repeat PCRs daily to every other day after clinical recovery and when Ct values approached 25. In symptomatic patients, day one of illness is the day of symptom(s) onset or the day of detection of SARS-CoV-2 by PCR, whichever earlier; in asymptomatic patients, day one of illness is the day of detection of SARS-CoV-2 by PCR. The study was reviewed and approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB Ref: 2020/00909).

Results

Between February 2020 to September 2021, there were 38 haemodialysis patients admitted for COVID-19 illness in our centre. The cases were clustered in 2 distinct waves, mirroring the general epidemiological pattern of COVID-19 infections in Singapore – only 4 individuals were admitted between April to May 2020 while 34 were admitted between May to September 2021. There were no COVID-19 haemodialysis cases between June 2020 to April 2021. The mean age of the patients is 63.9 ± 9.8 years, 61% female, and diabetic kidney disease and glomerulonephritis are the predominant causes of ESKD (Table 1). Baseline characteristics, clinical features and laboratory investigations at presentation were similar between subjects infected during delta-variant period, compared with pre-delta variant period, except for a significantly higher C-reactive protein level at presentation in subjects during pre-delta variant period. In subjects infected during the delta-variant period, baseline characteristics, clinical features and laboratory investigations at presentation were also similar between vaccinated and unvaccinated groups, except for more severe lymphopaenia in the unvaccinated group. Majority of infections were non-severe. However, 15 subjects (39%)

required oxygen supplementation, 23 (61%) had evidence of pneumonia on plain chest X-ray and 5 (13%) needed intensive care unit admission, during the course of the disease. There were 2 (5%) mortalities, both of which were unvaccinated individuals in delta-variant period COVID-19 infection.

Ct value rises progressively over the course of illness, as expected, with the largest rise after 1st week. (Figure 1A) In subjects infected during delta-variant period, Ct value at presentation (17.6 ± 1.0) was significantly lower compared with patients infected during pre-delta variant period (26.9 ± 5.6) ($p=0.01$), signifying a higher viral load at presentation in patients infected during delta-variant period (Figure 1B & Table 2). Patients infected during delta-variant period took a median duration of 28 [interquartile range (IQR) 23-31] days to achieve 2 negative swabs at least 24 hours apart, while patients infected during pre-delta variant period achieved 2 negative swabs at least 24 hours apart at median of 17 (IQR 11-23) days ($p=0.02$). However, the median days to achieve a Ct value of ≥ 25 was no different in patients infected during delta-variant period [9 (IQR 7-12) days], compared to pre-delta variant period [8 (IQR 4-13) days], $p=1.00$. Similarly, the median days to achieve a Ct value of ≥ 30 was not significantly different in patients infected during delta-variant period [13 (IQR 11-15) days], compared to pre-delta variant period [10 (IQR 4-18) days], $p=0.68$. The time to achieve a Ct value of ≥ 30 for patients during the delta variant period was similar to the general population with confirmed delta variant (B.1.617.2) infection in Singapore (13).

We further compared vaccinated against unvaccinated patients, infected during the delta variant period. There was no significant difference in the Ct value at presentation between the 2 groups (vaccinated 17.0 ± 1.0 versus unvaccinated 19.0 ± 2.4 , $p=0.37$). (Figure 1B)

However, vaccinated patients were able to achieve 2 negative swabs at least 24 hours apart 8 days earlier than unvaccinated patients [vaccinated median 24 (IQR 21-26) days versus unvaccinated median 32 (IQR 30-34) days] $P < 0.01$. There were no difference in the vaccinated versus unvaccinated groups in achieving Ct value of ≥ 25 or ≥ 30 .

Discussion

In this study, we found that haemodialysis patients infected during the delta-variant period have increased viral load at presentation and prolonged virus shedding following COVID-19 infection, with an increase of 11 days compared to pre-delta variant period. This observation is even more marked in the unvaccinated population, where patients take an average of one month or more to become negative on PCR testing. When considered with literature suggesting to await 2 negative PCR testing before de-isolating dialysis patients (14), this implies that haemodialysis patients infected with delta variant (especially the unvaccinated) will require prolonged isolation and has significant implications on utilisation of healthcare resources. Dialysis centres using a test-based regime to determine de-isolation of COVID-19 dialysis patients will then require each patient to remain isolated for an extended period of time. With many countries experiencing sequential waves of infection with the delta variant, the number of dialysis patients in a similar situation will continue to increase but yet most community dialysis facilities do not have adequate isolation dialysis facilities. Dialysis centres without adequate number of isolation dialysis facilities will need to make alternative arrangements, for example a dedicated dialysis facility, or require the patients to be hospitalised. Other important considerations of requiring 2 negative PCR testing before de-isolating dialysis patients include the strain on laboratory resources with repeated and

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frequent PCR testing, and patients' mental health when faced with prolonged isolation, when he or she feels well otherwise. Furthermore PCR may be positive in later illness when the patient is no longer infectious and even if a lower 'threshold' is adopted (e.g. inferring non-infectiousness when Ct values reach ≥ 25 or ≥ 30) there are numerous limitations which must be borne in mind, including the many pre-, intra- and post-analytic factors that affect Ct values (15) and all diagnostic tests pose limitations in inferring infectiousness (16). In the absence of a 'perfect' test however, Ct values may provide support for non-infectiousness as correlated by an inability to isolate replication-competent virus by culture (7). In turn, such data may inform duration-based de-isolation strategies, including special sub-populations with concern for impaired immunity, including haemodialysis patients, without the need of a repeat PCR as a pre-requisite for de-isolation.

Although the initial Ct values are similar in vaccinated and unvaccinated subjects, the effect of vaccination with a shorter duration of viral shedding has implications on transmissibility and infection control policy affecting dialysis provider. A shorter duration of infectivity will permit a shorter duration of isolation for vaccinated individuals. This may also suggest that vaccination reduces secondary transmission in dialysis centres and may impact wider infection prevention and control measures in haemodialysis patients, although this needs to be further studied.

However, despite prolonged virus shedding, our results also show that the time to achieve a high Ct value is similar in delta and non-delta variants or in vaccinated and un-vaccinated groups. Viral shedding has been shown to be prolonged in immunocompromised patients, including subjects with ESKD (5), but from our data, and extrapolating from data from other

studies which attempted viral culture, the high Ct value suggest that the viral shedding is likely comprised of non-viable viral fragments (7).

It is not surprising that individuals infected with the delta variant has a lower Ct value at presentation when compared to individuals previously infected with the non-delta variant, as has been shown previously in the general population, and which correlates with increased viral replication (17). This finding has been previously been described as a potential mechanism for increased transmissibility in delta variants, and may possibly be the same in haemodialysis patients.

To our knowledge, we provide the first data characterising the impact of vaccination and delta variant on virological dynamics in haemodialysis patients. Our study has several strengths. During the study period, Singapore adopted an active case finding and surveillance, where all patients with fever or respiratory symptoms, in addition to close contacts of confirmed cases, underwent screening for COVID-19 by PCR. In Singapore, all haemodialysis patients with COVID-19 illness are hospitalised for isolation and monitoring, with the great majority being admitted in our centre. Hence, we avoided selection bias by including patients with both mild and severe illness, and is able to obtain a unique cohort capturing the entire spectrum of disease severity, with representative viral load and kinetics, even though the number of patients in this study is relatively small. PCR is done routinely for all patients at presentation for diagnosis and thereafter at frequent intervals for monitoring. Ct value is reported routinely, and we were able to compare Ct values as sequential samples are performed on the same platform. The limitations of the study are that the viral load is inferred from Ct values of the PCR of swabs and the timing of the swabs is determined by the treating

physician, and not according to a strict protocol. Hence, the days to achieve consecutive negative swabs or Ct value of ≥ 25 and ≥ 30 may include a small margin of error, if the swabs are not performed on consecutive days. Lastly, we determined that viral shedding with a high Ct value is not viable based on current literature, but we did not perform virus culture in any of our samples. Of note, this study was performed in patients infected with the pre-delta and delta variants, and the results may not be generalisable to the current Omicron or other subsequent variant of concerns.

In conclusion, our study demonstrates that patients infected during delta-variant period of COVID-19 illness, have higher viral load at presentation and prolonged viral shedding, especially in the unvaccinated cohort. However, all patients, including delta vs non-delta variants and vaccinated vs unvaccinated persons, were similar in reaching a high Ct value. These results provide nephrologists and dialysis providers insights into the dynamics of viral transmission of COVID-19 illness, in the era of delta variant and vaccination.

Tables

	All (n=38)	Pre-delta variant (n=4)	Delta variant (n=34)	Delta variant	
				Unvaccinated (n=10)	Vaccinated (n=24)
Age, years (\pm SD)	63.9 (\pm 9.8)	65.0 (\pm 6.0)	63.7 (\pm 1.7)	65.6 (\pm 4.0)	63.0 (\pm 1.7)
Female, n (%)	23 (61)	3 (75)	20 (59)	5 (50)	15 (63)
Cause of end stage kidney disease, n (%)					
Diabetes mellitus	19 (50)	2 (50)	17 (50)	4 (40)	13 (54)
Glomerulonephritis	13 (34)	2 (50)	11 (32)	3 (30)	8 (33)
Hypertension	3 (8)	0 (0)	3 (9)	2 (20)	1 (4)
Others	3 (8)	0 (0)	3 (9)	1 (10)	2 (8)
Co-morbidities, n (%)					
Diabetes mellitus	22 (58)	2 (50)	20 (59)	6 (60)	14 (58)
Hypertension	31 (82)	4 (100)	27 (79)	9 (90)	18 (75)
Ischaemic heart disease	19 (50)	1 (25)	18 (53)	7 (70)	11 (46)
Malignancy	6 (16)	0 (0)	6 (18)	1 (10)	5 (21)
Mean duration of dialysis vintage, years (\pm SD)	5.1 (\pm 4.8)	5.0 (\pm 1.5)	5.1 (\pm 0.9)	5.7 (\pm 1.3)	4.8 (\pm 1.1)
AVF as dialysis vascular access, n (%)	31 (82)	4 (100)	27 (79)	8 (80)	19 (61)
Use of ACEi or ARBs at onset of COVID-19 illness, n (%)	11 (29)	2 (50)	9 (26)	4 (40)	5 (21)
Fever at presentation, n (%)	16 (42)	2 (50)	14 (41)	7 (70)	7 (29)
Pneumonia at presentation, n (%)	13 (34)	1 (25)	12 (35)	4 (40)	8 (33)
Pneumonia during illness, n (%)	23 (61)	2 (50)	21 (62)	9 (90)	12 (50)
Requires oxygen supplementation, n (%)	15 (39)	2 (50)	13 (38)	6 (60)	7 (29)
ICU admission, n (%)	5 (13)	2 (50)	3 (9)	2 (20)	2 (4)
Mortality, n (%)	2 (5)	0 (0)	2 (15)	2 (20)	0 (0)
Haemoglobin, g/dL (\pm SD)	10.8 (\pm 1.3)	10.8 (\pm 0.3)	10.8 (\pm 0.2)	10.7 (\pm 0.5)	10.9 (\pm 0.3)
White blood cell, x 10 ⁹ cells/L (\pm SD)	6.6 (\pm 2.3)	7.5 (\pm 1.3)	6.5 (\pm 0.4)	6.0 (\pm 0.6)	6.8 (\pm 0.5)
Lymphocytes, 10 ⁹ cells/L (\pm SD)	1.15 (\pm 0.52)	1.21 (\pm 0.31)	1.14 (\pm 0.09)	0.84 (\pm 0.11) ^a	1.27 (\pm 0.11) ^a
C-reactive protein, mg/L (\pm SD)	31.7 (\pm 45.6)	118.4 (\pm 44.2) ^b	21.2 (\pm 4.1) ^b	23.8 (\pm 9.9)	20.2 (\pm 4.4)
Lactate dehydrogenase, U/L (\pm SD)	448.3 (\pm 126.7)	522.3 (\pm 92.6)	439.6 (\pm 20.4)	447.6 (\pm 37.1)	436.2 (\pm 24.9)

^ap=0.02, ^bp<0.001, p >0.05 (not significant) unless specified

ACEi, angiotensin converting enzymes inhibitor; ARB, angiotensin II receptor blocker; AVF, arterio-venous fistula; SD, standard deviation

Table 1: Baseline characteristics and outcomes of individuals during delta-variant and pre-delta variant period, and vaccinated and unvaccinated individuals.

	All (n=38)	Pre-delta variant (n=4)	Delta variant (n=34)	Delta variant	
				Unvaccinated (n=10)	Vaccinated (n=24)
Ct value at presentation	18.5 (\pm 7.0)	26.9 (\pm 5.6) ^a	17.6 (\pm 1.0) ^a	19.0 (\pm 2.4)	17.0 (\pm 1.0)
Median number of days to achieve 2 consecutive negative swabs, days (IQR)	25 (21-30)	17 (11-23) ^b	28 (23-31) ^b	32 (30-34) ^c	24 (21-26) ^c
Median number of days to achieve Ct \geq 30, days (IQR)	13 (10-15)	10 (4-18)	13 (11-15)	13 (13-17)	13 (10-13)
Median number of days to achieve Ct \geq 25, days (IQR)	9 (7-13)	8 (4-13)	9 (7-13)	13 (5-13)	9 (7-11)

^ap=0.01, ^bp=0.02, ^cp<0.01, p >0.05 (not significant) unless specified

Ct, cycle threshold; IQR, inter-quartile range

Table 2: Virological dynamics as measured by the polymerase chain reaction cycle threshold value in different sub-group of patients.

Figure legend

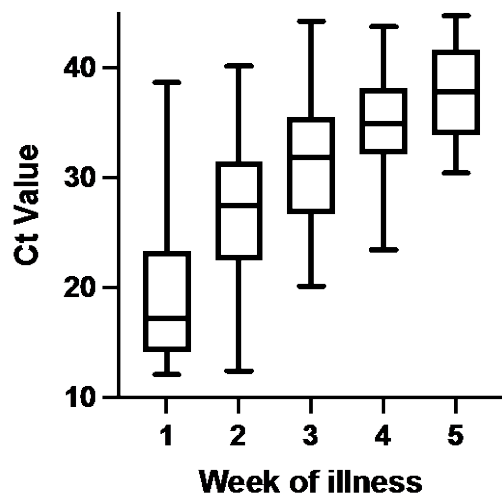
Figure 1

A. Trend of polymerase chain reaction cycle threshold (Ct) values during the course of illness in 38 haemodialysis patients. The rise in Ct values is most marked after the first week of illness, after which the Ct values continue to increase, but at a slower rate. A small proportion of patients continue to remain PCR positive at week 4 and 5 of illness, albeit with a higher Ct value.

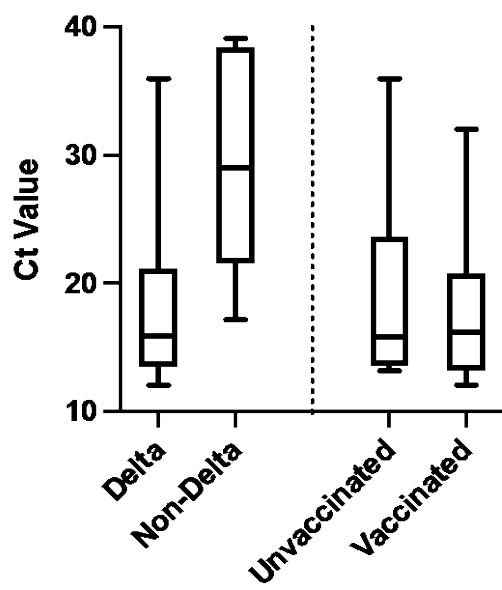
B. Cycle threshold (Ct) values at onset of illness, comparing delta-variant period vs pre-delta variant period and unvaccinated vs vaccinated individuals. Ct value at onset of illness was significantly lower in patients infected during delta-variant period, compared with patients infected during pre-delta variant period, signifying a higher viral load at presentation in patients infected during delta-variant period. However, the Ct values were similar in vaccinated and unvaccinated individuals, during delta-variant period.

Figure 1

A.



B.



Compliance with Ethical Standards:

Funding: This study was not supported by any external funding.

Conflict of Interest: All authors declare that there is no conflict of interest.

Data available on request.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was reviewed and approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB Ref: 2020/00909).

Informed consent: Waiver of informed consent was granted by the institutional review board National Healthcare Group Domain Specific Review Board for all individual participants included in the study.

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