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MAIN TEXT

The changing pattern of COVID-19 infection in hemodialysis and peritoneal dialysis patients

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Abstract

Introduction: Following the first wave of COVID-19 there have been several variants. We wished to review the number and severity of infections with the different variants in a population of hemodialysis (HD) and peritoneal dialysis (PD) patients.

Methods: We reviewed the outcomes and results in HD and PD patients testing positive for COVID-19 between March 2020 and August 2022.

Results: Seven hundred and ninety-five cases of COVID-19 were recorded in 710 dialysis patients. More HD patients than PD contracted wild type (21.4% vs. 6.8%), delta (23.3% vs 6.3%), and omicron (27.7% vs. 14.7%), all $p < 0.01$, but no difference with alpha (4.6% vs. 6.3%) or beta variants (5.7% vs. 6.85%). Hospitalization and death were greatest for alpha followed by wild type, beta, delta, and omicron (60.6% vs. 57% vs. 47.5% vs. 21.2% vs. 19.3%), respectively, $p < 0.001$. C reactive protein progressively increased from outpatient management to hospitalization to hospitalization with critical care or death (14 (4–30) vs. 41 (18–101) vs. 94 (47–168) mg/L, $p < 0.001$. Despite previous infection and vaccination 85 (12%) patients had two or more infections with COVID-19.

Conclusion: Disease severity declined and survival improved as the virus mutated from wild-type and alpha to beta, delta, and omicron variants. Whether this related to reduction in viral virulence, vaccination, natural acquired immunity, or introduction of pharmacological treatments remains to be determined. Government lockdowns and enhanced infection control measures reduced the percentage of HD patients contracting alpha and beta variants to that of PD. Vaccination and prior infection did not prevent reinfection.

KEYWORDS

COVID-19, hemodialysis, hospitalization, inflammation, peritoneal dialysis, survival

1 | INTRODUCTION

Hemodialysis (HD) patients are potentially at increased risk of contracting COVID-19, due to attending dialysis centers for treatment and spending time in the proximity to other patients and members of the dialysis nursing staff, in buildings which have poor quality ventilation, and sharing communal waiting areas and transport to and from dialysis centers.[1,2] Initial reports also suggested a higher mortality for HD patients,[1] but this may have been

exacerbated by the higher underlying comorbidity and frailty of the HD population and the acute severe demand on health care resources.[3,4]

On the other hand, peritoneal dialysis (PD) being a home-based therapy does not potentially expose patients to greater risks of contracting COVID-19 compared to the haemodialysis population, and several studies have reported both a lower incidence of COVID-19 infections in PD patients and lower mortality.[5,6] However, as many HD centers introduced COVID-19 enhanced infection control measures during the first wave of COVID-19 infection, designed to reduce the rate of transmission between patient infection rates remained high.[7] These changes in clinical practice coupled with the introduction of vaccination programs,[8] have been reported to reduce infection rates[9] and mortality.[10]

Following the first wave of the wild-type COVID-19 virus spread from Wuhan in China, we have experienced several other variants including alpha, beta, delta, and more recently omicron. As such, we wished to review our experience of these COVID-19 variants in HD and PD patients, both in terms of prevalence and clinical disease severity.

2 | PATIENTS AND METHODS

In March 2020, when the first COVID-19 cases were identified then testing for COVID-19 was initially restricted to symptomatic patients, needing hospital admission. Nasal and pharyngeal swabs were tested by COVID-19 real-time reverse transcriptase-polymerase chain reaction (RT-PCR), initially by the UK Public Health Service laboratory, then subsequently by a UK approved immunoassay (Roche Cobas Immunoassay platform, Roche Diagnostics Ltd, Burgess Hill, UK). United Kingdom (UK) approved nasal or nasopharyngeal, COVID-19 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test.[11] Patients attending for HD outpatient treatments were then routinely screened for COVID-19 whether symptomatic or not, whereas PD patients were only initially screened when symptomatic, and then as part of community contact tracing programs or when attending hospital clinics for review, and then when home testing programs were rolled out to the general public.[12]

In London the predominant COVID-19 variant was the original wild type between March and July 2020, then alpha from August to December 2020, beta from January to May 2021, delta June to December 2021, and then from January 2022 omicron variants. HD and PD patients were at increased risk of COVID-19 and so offered a first vaccination against COVID-19 in February–March 2021, and then a second vaccination in April–May 2021, either ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca, Macclesfield, UK) or BNT162b2 (BioNTech, Pfizer, Mainz, Germany).

In addition to standard hematological and biochemistry testing for C reactive protein (CRP), N-terminal brain natriuretic peptide (NTproBNP), ferritin, and troponin T (TnT) were taken concurrently and analyzed in an accredited United Kingdom laboratory by standard methods (XE-2100 Sysmex Corporation, Kobe, Japan; ECLIA Roche Diagnostics, GMBH, Mannheim, Germany).[13] In view of the reports of excessive clotting with COVID-19,[14] samples were also analyzed for fibrinogen and D-dimers. Clauss fibrinogen was measured using a HemosIL Recombiplastin 2G and D-dimers using the Innovance D-dimer test (Siemens Healthcare Diagnostics, Marburg, Germany) on a CS5100 (Sysmex, Corporation, Kobe, Japan).[15]

2.1 | Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Standard statistical analyses were used: D'Agostino and Pearson normality test, Chi-square, *t* test, Mann–Whitney U test, ANOVA with appropriate post-hoc Bonferroni or Games–Howell correction. Statistical analysis was performed using Graph Pad Prism (version 9.2, Graph Pad, San Diego, CA, USA), Statistical Package for Social Science version 28.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken at or below the 5% level.

2.2 | Ethics

This study complied with UK National Research Ethical standards for clinical practice development and audit, with data collected as part of NHS ethics committee 20/SW/0077, with all data appropriately anonymized.

3 | RESULTS

Between March 2020 and August 2022, a total of 795 cases of COVID-19 were recorded in 710 dialysis patients. Most cases (90%) occurred in HD patients (Table 1), with significantly more HD than PD patients testing positive for the wild-type, delta, and omicron variants (Figure 1). Seventy HD patients (11%), and five PD patients (6.8%) had two COVID-19 infections (5 alpha, 17 delta, and 60 omicron), and 5 (0.8%) HD patients had three separate infections (one with delta and four with omicron).

Most infections occurred when omicron was the predominant variant in the community, followed by delta

TABLE 1 Patients divided according to COVID-19 variants.

Variable	Wild type	Alpha	Beta	Delta	Omicron
Number	179	51	58	241	322
Male %	64.8	64.7	60.3	58.1	64.9
Age years	63.8 ± 16.5	65.1 ± 14.7	63.3 ± 13.6	61.7 ± 16.3	64.0 ± 13.7
HD %	92.1	80.4	81.4	91.2	90.0
Hb g/L	105.4 ± 18.2	104.0 ± 16.8	109.8 ± 16.2	112.8 ± 5.5	116.7 ± 10.2
PMN $\times 10^9$/L	4.4 (3.0–7.1)	4.0 (2.9–5.4)	3.3 (2.4–5.3)	4.0 (2.9–5.4)	4.0 (2.1–5.6)*
PBL $\times 10^9$/L	0.7 (0.5–1.2)	0.9 (0.5–1.2)	1.0 (0.7–1.4)	1.1 (0.8–1.6)**	1.1 (0.7–1.6)**
Plts $\times 10^9$/L	184 (138–232)	174 (141–235)	183 (147–231)	195 (151–242)	198 (151–251)
CRP mg/L	41 (12–104)	41 (10–132)	23 (7–65)	15 (10–36)**	14 (5–40)**
Ferritin ug/L	1080 (507–1744)	827 (394–1794)	769 (377–1194)	566 (322–981)	602 (289–1013)
BNP pg/mL	5718 (1760–28 614)	8819 (2532–27 273)	6153 (2587–30 124)	4890 (1928–18 499)	6707 (2596–26 329)
TnT pg/mL	107 (56–169)	85 (50–160)	88 (60–144)	67 (44–119)	72 (40–120)
INR	1.1 ± 0.3	1.3 ± 0.8	1.4 ± 1.4	1.1 ± 0.5	1.1 ± 0.6
APTTs	35 (30–40)	34 (31–41)	34 (31–45)	34 (30–39)	33 (30–37)
Fibrinogen g/L	5.02 ± 1.43	5.27 ± 1.57	5.08 ± 1.47	4.65 ± 1.5	4.51 ± 1.58*
D-dimer ng/mL	1472 (858–2975)	1532 (857–3727)	1257 (709–2703)	1086 (609–2956)	1187 (619–2150)

Note: Patient demographics and laboratory investigations obtained when patients first tested positive for COVID-19. Values expressed as integer, percentage, mean ± standard deviation, median (interquartile range). *$p < 0.05$, **$p < 0.001$ versus wild-type COVID-19 variant.

Abbreviations: APTT, activated partial thromboplastin time; BNP, N-terminal pro-brain natriuretic peptide; CRP, C reactive protein; Hb, hemoglobin; HD, Hemodialysis; INR, international normalized ratio; PBL, peripheral blood lymphocyte; Plts, platelets; PMN, peripheral blood leukocyte/neutrophil; TnT, troponin T.

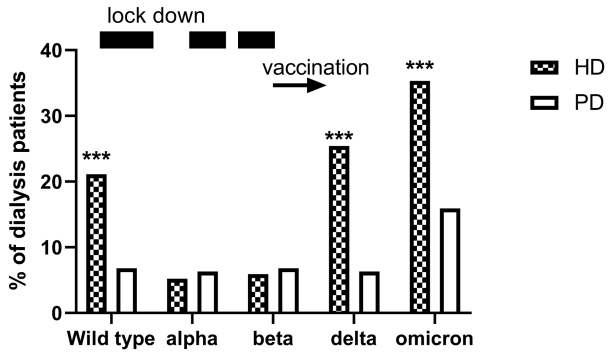

FIGURE 1 Percentage of hemodialysis (HD) and peritoneal dialysis (PD) patients testing positive for COVID-19 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and the predominant COVID-19 variant at the time of testing. UK government lockdowns marked along with first and second vaccinations. **$p < 0.001$, ***$p < 0.001$ versus PD.

(Table 1). However, more patients died or required hospital admission with the wild-type or alpha variants (Figure 2). In terms of laboratory results, then there was less systemic inflammation with omicron and delta variants compared to the wild type in terms of lower polymorphonuclear leukocytes (PMN), CRP, and fibrinogen, whereas peripheral blood lymphocytes (PBLs) were greater. However, there were no differences in ferritin, D-dimer, international normalized ratio (INR), or activated partial thromboplastin time (APTT). Similarly, there were no statistical differences in NTproBNP or TnT (Table 1).

Categorizing patients according to disease severity, then patients who died or required intensive care (ICU) support had higher PMN, CRP, fibrinogen, D-dimers, and both NTproBNP and TnT compared to those did not require hospitalization, and lower hemoglobin, and PBL (Table 2).

4 | DISCUSSION

Overall, 13.4% of our patients required ICU support or died. Clinical severity of infection was greatest with the earlier wild-type and alpha COVID-19 variants compared to the later omicron variants, in keeping with reports of greater than 20% mortality for HD patients during the first wave of the pandemic.[3,6] In keeping with severity of the clinical presentation, laboratory investigations showed a greater inflammatory response, characterized by differences in PMN, PBL, CRP, but also markers of cardiovascular damage, NTproBNP and TnT, and activation of coagulation

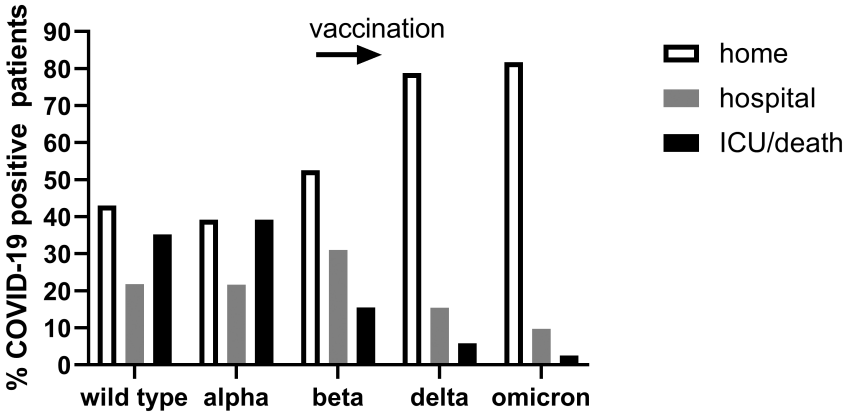

FIGURE 2 Number of patients dialysis testing positive for COVID-19 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) who were managed as outpatients (home), required hospitalization but no intensive care support (hospital) and those requiring intensive care support or died (ICU/death) and predominant COVID-19 variant at the time of testing. UK government first and second vaccinations marked. Wild-type variant versus delta and omicron $p < 0.001$. Alpha variant versus delta and omicron $p < 0.001$. Beta variant versus delta $p = 0.012$, versus omicron $p = 0.002$.

TABLE 2 Patients divided according to disease severity.

Variable	Home	Hospital	ICU/died
Number	581	156	114
Male %	61.5	60.9	70.2
Age years	61.4 ± 14.7	63.7 ± 15.8	70.1 ± 13.1
HD %	93.4	74.6**	90.4
Hb g/L	116.0 ± 18.3	105.4 ± 19.1	100.2 ± 19.1**
PMN $\times 10^9$/L	3.69 (2.65–4.99)	5.15 (3.49–5.77)*	5.58 (3.98–8.42)**
PBL $\times 10^9$/L	1.17 (0.81–1.58)	0.79 (0.53–1.2)**	0.85 (0.4–0.92)**
PLts $\times 10^9$/L	193 (151–236)	197 (155–271)	180 (118–242)
CRP mg/L	14 (4–30)	41 (18–101)**	93 (47–168)**
Ferritin ug/L	561 (297–926)	1011 (587–1969)**	1195 (737–2454)**
BNP pg/mL	4879 (11 936–16 960)	8212 (2766–31 203)*	13 126 (3572–37 926)**
TnT pg/mL	63 (40–115)	95 (65–155)	153 (86–313)**
INR	1.1 ± 0.7	1.2 ± 0.6	1.1 ± 0.6
APTTs	33 (31–37)	34 (30–41)	37 (32–44)
Fibrinogen g/L	4.41 ± 1.4	5.48 ± 1.61**	5.34 ± 1.45**
D-dimer ng/mL	1055 (585–1814)	1583 (892–3358)*	3266 (1437–6956)**

Note: Patients not requiring hospitalization (home), hospitalization but not requiring intensive care support (hospital) and those requiring intensive care support or died (ICU/died). Patient demographics and laboratory investigations. Values expressed as integer, percentage, mean ± standard deviation, median (interquartile range). *$p < 0.01$, **$p < 0.001$ versus patients not requiring hospitalization (home).

Abbreviations: APTT, activated partial thromboplastin time; BNP, N-terminal pro-brain natriuretic peptide; CRP, C reactive protein; Hb, hemoglobin; HD, Hemodialysis; INR, international normalized ratio; PBL, peripheral blood lymphocyte; Plts, platelets; PMN, peripheral blood leukocyte/neutrophil; TnT, troponin T.

with increased fibrinogen and D-dimers. These results are in keeping with other reports in non-dialysis populations, with greater rises in TnT and NTproBNP, being associated with worse outcomes.[16,17] COVID-19 is recognized to cause a myocarditis, which has also been occasionally reported after vaccination using a vaccine based on the spike protein. Similarly, COVID-19 infections are associated with an increased risk of clotting, and both fibrinogen and D-dimers have also been observed to reflect more clinically severe disease.[18,19]

Although clinical disease severity and laboratory markers of inflammation were less with the omicron variants compared to original wild-type COVID-19, other factors than changes in viral virulence have to be considered. In the UK nonhospitalized but symptomatic dialysis patients have been eligible for anti-COVID 19 medications, molnupiravir, and sotrovimab as outpatients from December 2021. Vaccination of dialysis patients started during COVID-19 beta wave of infections, and patients were offered a first and second vaccination before the next wave with the delta variant. Although HD patients make a lower response to vaccination than then general population,[8] studies have reported a reduction in clinical severity in vaccinated patients,[9] but these results may be confounded by viral variants of lower pathogenicity, and partial immunity from previous COVID-19 infections. Patients were offered a third, or booster vaccination in September–October 2021. However, we noted an increase in the number of COVID-19 infections with the omicron variants despite patients having up to three vaccinations. This is in keeping with studies reporting 38% of HD patients with two vaccinations contracting COVID-19, and no additional effect of a booster in reducing infections, with infection rates of 39% observed.[10] Eighty-five of our patients contracted COVID-19 two or three times. Seven of these patients (23.5%) were recorded as refusing vaccination, although the majority (65.9%) were documented to have two or more vaccinations, with the remainder who may have been vaccinated by their family doctor practice. As such, previous infections and vaccinations do not necessarily prevent reinfection. However, recent reports from China have suggested that effective vaccination does play a major role in reducing morbidity and mortality from omicron COVID-19 infections (personal communication Professor X Ding).[20]

Most reports of COVID-19 infections in dialysis patients have concentrated on HD patients.[1,3] One study from Wuhan province in China reported <1% of PD patients contracting COVID-19.[5] We noted a major difference in the proportion of HD patients contracting COVID-19 compared to PD patients, particularly during the first pandemic wave with the wild-type variant, and then more latterly with the delta and omicron variants. HD patients are at greater risk of contracting air borne pathogens compared to PD patients, due to the congregation of HD patients in communal waiting areas, communal transport, and dialyzing in centers with inadequate ventilation.[21] Most HD centers introduced enhanced infection control measures and increased the use of personal protective equipment to reduce the risk of infection for HD patients.[7] In addition to these measures and vaccinations offered to patients, the UK government introduced a number of lockdowns. First, April to June 2020, followed by November to December 2020 and finally January to March 2021, when the COVID-19 variants were predominantly wild type, alpha, and beta, respectively. The combination of enhanced infection control practices and statutory lockdowns may have accounted for the reduction in infections observed in our HD patients down to comparable levels to PD patients during the times when alpha and beta variants were circulating. However, there was an increase in infections in the HD patients with delta and then omicron variants. This may have been due to a combination of viral variants with enhanced transmissibility and relaxation of some of the stricter infection control measures.[22]

The first pandemic wave of COVID-19 resulted in a much greater infection rate for HD patients compared to PD, associated with an increased requirement for hospitalization and ICU support, with a correspondingly high mortality. Government lockdowns and enhanced infection control measures reduced infection rates with alpha and beta variants in HD patients. The combination of vaccination, natural immunity from previous infections, pharmacological treatments, and changes in viral variant virulence have all led to a reduction in hospital and ICU admissions, and mortality. However, vaccination and previous infection do not prevent de-novo infections with the current more transmissible variants.

AUTHOR CONTRIBUTIONS

Cate Goodlad organized COVID-19 testing and reporting program, supervised infection control policies, organized outpatient treatment of COVID-19 infections, and approved the final version. Andrew Davenport conceived the audit, analyzed the data, and wrote the first draft manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data held UCL Department of Nephrology V drive, data availability upon reasonable request and within NHS guidelines.

ETHICS STATEMENT

Retrospective audit approved by UK National Research Ethics Services (NRES) committee 20/SW/0077.

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