


The effect of prescribing vitamin D analogues and serum vitamin D status on both contracting COVID-19 and clinical outcomes in kidney dialysis patients'

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Abstract

Aims: Vitamin D plays a role in innate immune system activation, and deficiency increases susceptibility to respiratory infections and disease severity including COVID-19. We determined whether vitamin D levels and medications were associated with contracting COVID-19, and disease severity defined by hospitalisation and dialysis patient mortality.

Methods: We reviewed serum vitamin D levels, and prescription of cholecalciferol and alfacalcidol along with corresponding medical records of adult dialysis patients from a United Kingdom tertiary centre between March 2020 and May 2021. COVID-19 infection was determined by polymerase chain reaction (PCR) results.

Results: 362 (35%) of 1035 dialysis patients tested PCR positive for COVID-19. COVID-19 positive patients had lower native median vitamin D (65 (39–95) versus 74 (40.5–101) nmol/L ($p = .009$) despite greater prescription of cholecalciferol (median 20 000 (20000–20 000) versus 20 000 (0–20 000) IU/week), $p < .001$, but lower prescription of alfacalcidol 0 (0–3.0) versus 2.0 (0.–5.0) ug/week, $p < .001$. On multivariate logistic regression COVID-19 infection was associated with haemodialysis versus peritoneal dialysis ($p < .001$), cholecalciferol dose ($p < .001$) and negatively with alfacalcidol ($p < .001$). However, serum vitamin D levels and alfacalcidol dosages were not significantly different for those requiring hospitalisation compared to those managed at home, although those who died were prescribed lower alfacalcidol dosages.

Conclusion: Dialysis patients who contracted COVID-19 had lower levels of native vitamin D prior to COVID-19 and were prescribed lower dosages of alfacalcidol. However, there was no association between vitamin D status and disease severity. This retrospective observational analysis supports a potential role for vitamin D and susceptibility to COVID-19 infection in dialysis patients.

KEYWORDS

co-morbidity, COVID-19, haemodialysis, frailty, peritoneal dialysis, vitamin D

SUMMARY AT A GLANCE

Vitamin D plays a key role in activating the innate immune system and deficiency increases susceptibility to respiratory infections. We report on the effect of vitamin D levels and medications in more than 1000 dialysis patients during the first two pandemic waves of COVID-19.

1 | INTRODUCTION

The majority of immune cell types, particularly antigen-presenting cells (APCs) including monocytes, macrophages, and dendritic cells express vitamin D receptors (VDR) on their cell surface.¹ Activation of the VDR by 1,25 (OH)₂D₃ leads to the release of antimicrobial peptides, cathelicidin as well as beta defensins which attack pathogens.² Although vitamin D enhances the innate immune system, it can also down regulate the adaptive immune system by effecting T helper type 2 lymphocytes.³ There has been debate as to whether vitamin D deficiency, or supplementation with 25 (OH)D₃ alters the risk of contracting infection, or the severity of infection. A recent meta-analysis suggested that vitamin D supplementation of 10–25 ug/day reduced the risk of acute respiratory tract infections.⁴

COVID-19 is a respiratory infection, and there have been a number of observational studies reporting on the association between serum vitamin D concentrations and disease severity. One study reported greater disease severity in vitamin D deficient patients,⁵ and another greater morbidity and mortality for older patients with low levels of vitamin,⁶ whereas the administration of large doses of vitamin D was associated with a reduction in the duration of hospital admissions.⁷ Epidemiological studies reported less COVID-19 positivity in the US population with greater vitamin D levels.⁸

Patients with chronic kidney disease have been reported to have reduced levels of both 25(OH)D₃ and 1,25 (OH)₂D₃,⁹ and observational studies have suggested that dialysis patients are at greater risk of contracting COVID-19.¹⁰ We therefore wished to review whether there was any association between serum vitamin D levels or prescription of vitamin D medications in our haemodialysis (HD) and peritoneal dialysis (PD) patients and COVID-19 infection or disease severity.

2 | METHODS AND PATIENTS

We collected laboratory data, demographics, medical histories, and prescribed medications from the electronic medical records of all patients under the care of a university dialysis programme during the two waves of COVID-19 infections between March 2020 and May 2021. From mid-April 2020 routine screening of all HD outpatients was introduced, whereas PD patients were only tested if symptomatic or prior to any routine or emergency hospital admission, or as part of the United Kingdom (UK) National Health Service (NHS) community testing programmes. Review of records included current and previous prescription of immunosuppressive treatment. Patients with failed transplants who had returned dialysis were prescribed prednisolone, median dose 5 (0–5) mg/day and tacrolimus 0 (0–2) mg/day, and other patients were noted to have had previously been given immunosuppression for various conditions including glomerular diseases, vasculitis, antglomerular basement membrane disease, systemic lupus erythematosus, and renal transplantation. However, historic records were often unclear as to the amounts and duration of immunosuppressive treatment prescribed, and as such these patients were categorised as having received historic immunosuppressive treatment.

In addition to standard laboratory investigations, we measured ferritin, C reactive protein (CRP) and N-terminal probrain natriuretic peptide (NT-proBNP) at the time of testing positive for COVID-19 as part of a standard set of investigations for patients testing positive for COVID-19, and 25 hydroxyl vitamin D₃ (25VitD) was obtained from the results prior to testing positive for COVID-19, using an immunoassay (Roche Cobas Immunoassay platform, Roche Diagnostics Ltd, Burgess Hill, UK). Patient comorbidity was graded using the Charlson index adjusted not to include the age factor,¹¹ and in keeping with UK NHS holistic health care policy all patients were graded for frailty using the Rockwood frailty score.¹²

2.1 | Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, and percentage. Data was analysed using the D'Agostino & Pearson normality test, and numerical data was analysed by t test if normally distributed or by Mann Whitney U test if nonparametric data. Categorical data was analysed using the Chi square test (X²). Appropriate corrections for small numbers and multiple testing, were applied for these statistical analyses. We then performed univariable logistic regression analysis between patients who tested positive for COVID-19 and those who did not contract COVID-19, and also for those patients with COVID-19 who required hospital admission and those with COVID-19 who did not require hospital admission. These models included age, sex, modality, adjusted Charlson comorbidity score without age and renal score, Rockwood clinical frailty score, current immunosuppressive therapy, cholecalciferol and alfacalcidol dosages, and serum 25VitD, NT-proBNP and ferritin concentrations. Finally, multivariable analyses were then performed by logistic regression. If variables were not normally distributed, then variables were log transformed to improve variable distribution. Statistical analysis was performed using Graph Pad Prism (version 9.0, Graph Pad, San Diego, CA, USA), Statistical Package for Social Science version 26.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken at or below the 5% level.

2.2 | Ethics

A national research ethics committee (NRES) 20/SW/0077 approved the collection of data from COVID-19 patients. Retrospective analysis of data complied with NRES regulations for audit and service development, with all patient data appropriately anonymised.

3 | RESULTS

Three hundred and sixty-two dialysis patients (35%) tested PCR positive for COVID-19 between March 2020 and May 2021 (Table 1). Patients who contracted COVID-19 had higher comorbidity and frailty scores, and were prescribed more cholecalciferol, but had lower

TABLE 1 Demographics, standard laboratory investigations and medications of dialysis patients, according to whether patients had tested positive for COVID-19. Data expressed as integer, percentage, mean \pm standard deviation, or median and interquartile range

Variable	Covid positive	Covid negative	p-value
Number	362	673	
Male/female	222/140	415/258	.941
Age, years	63.3 \pm 15.3	63.4 \pm 15.2	.975
Frailty score	4.6 \pm 1.4	4.3 \pm 1.4	.002
Charlson comorbidity	4.4 \pm 1.8	4.1 \pm 1.8	.037
Haemoglobin, g/L	105 (95–114)	107 (97–117)	.005
Albumin, g/L	34.8 \pm 5.3	36.7 \pm 6.9	<.001
C reactive protein, mg/L	8 (3–18)	7 (2–18)	.15
N-terminal probrain natriuretic peptide, ng/L	4162 (1604–15 173)	4247 (1525–1378)	.634
Ferritin, ug/L	447 (257–767)	476 (279–723)	.742
25 OH vitamin D, nmol/L	65 (39–95)	74 (40.5–101)	.009
Cholecalciferol, IU/week	20 000 (20 000–20 000)	20 000 (0–20 000)	<.001
Alfacalcidol, ug/week	0 (0–3)	2 (0–5)	<.001
Parathyroid hormone, pg/mL	35.0 (19.4–69.1)	34.3 (17.8–55.3)	.048
Current immunosuppression (%)	19 (5.2)	36 (5.3)	.95
Historic immunosuppression (%)	76 (21.0)	183 (27.2)	.028

Note: To allow analyse the effect of age, the Charlson comorbidity score has been calculated without the age factor.

TABLE 2 Comparison between haemodialysis (HD) and peritoneal dialysis (PD) patients testing positive or negative for COVID-19. Demographics, standard laboratory investigations and medications; C reactive protein (CRP), N-terminal probrain natriuretic peptide (NT-proBNP), 25 OH vitamin D (25VitD). Data expressed as integer, percentage, mean \pm standard deviation, or median and interquartile range

Variable	HD COVID-19 positive	HD COVID-19 negative	PD COVID-19 positive	PD COVID-19 negative
Number	331	519	31	154
Age, years	63.6 \pm 15.0	63.9 \pm 15.1	61.7 \pm 18.8	62.0 \pm 15.2
Male/female	204 (61.6%)/127 (38.4%)	332 (64%)/187 (36%)	18 (58.1%)/13 (41.9%)	83 (53.9%)/71 (46.1%)
Haemoglobin, g/L	105 (95–114)	108 (97–118)***	106 (98–120)	104 (96–115)
CRP, mg/L	9 (3–18)	8 (3–19)	5.5 (2–15)	5 (2–15)
NT-proBNP, ng/L	4426 (1593–6127)	4327 (1636–13 697)	3111 (1829–5706)	4136 (1150–14 726)
Ferritin, ug/L	447 (271–777)	456 (269–697)	373 (178–692)	534 (323–955)
25VitD, nmol/L	66 (40–97)	74 (39–105)	54 (30–74)	74 (50–91)**
Cholecalciferol, IU/week	20 000 (20 000–20 000)	20 000 (0–20 000)***	11 200 (0–20 000)	20 000 (20 000–20 000)***
Alfacalcidol, ug/week	0 (0–3.0)	2.5 (0.5–5.0)***	0 (0–0.88)	1.0 (0–3.5)**

* $p < .05$, ** $p < .01$, *** $p < .001$ versus COVID-19 positive patients.

haemoglobin, serum albumin and 25VitD, and were prescribed less alfacalcidol. Parathyroid hormone (PTH) levels were marginally, but statistically significantly higher in those patients testing positive for COVID-19. There were no differences in whether patients were prescribed current immunosuppressants, including steroids, but fewer patients who contracted COVID-19 had previously been prescribed immunosuppressive treatments (Table 1). Significantly more HD patients tested positive for COVID-19, than PD patients (Table 2). HD patient who contracted COVID-19 had significantly lower haemoglobin and were prescribed significantly lower doses of alfacalcidol, but greater doses of cholecalciferol. PD patients who

tested positive for COVID-19 were prescribed lower doses of both alfacalcidol and cholecalciferol.

In the UK, patients with a serum 25VitD level of 75 nmol/L are considered to have adequate levels,¹³ and more patients, who contracted COVID-19 had lower 25VitD levels. For peritoneal dialysis (PD) patients, 62.5% testing positive for COVID-19 had lower 25VitD levels compared to 31% of those who remained COVID negative (X2 13.8, $p = .001$). Similarly for the haemodialysis (HD) patients, 49.6% of those testing positive for COVID-19 had lower 25VitD levels, compared to 26.3% of those who remained COVID-19 free (X2 46.9, $p < .001$). Some 34.9% of male patients and 35% of female

TABLE 3 The effect of disease severity of patients testing for positive for COVID-19, in terms of whether patients required acute hospital admission (inpatient) or were managed at home (outpatient) or died. Demographics, standard laboratory investigations and medications of patients requiring hospital admission and those who died. Haemoglobin (Hb), C reactive protein (CRP), N-terminal probrain natriuretic peptide (NT-proBNP), 25 OH vitamin D (25VitD). Data expressed as integer, percentage, mean \pm standard deviation, or median and interquartile range

Variable	Inpatient	Outpatient	Died	Survived
Number	201	161	73	289
Age, years	67.0 \pm 14.5	60.3 \pm 15.5***	73.2 \pm 11.5	61.8 \pm 15.4***
Male/female	130/71	92/69	52/21	170/119
Charlson	4.6 \pm 1.9	4.1 \pm 1.7**	5.1 \pm 1.9	4.2 \pm 1.8***
Frailty score	4.9 \pm 1.5	4.4 \pm 1.6**	5.4 \pm 1.29	4.49 \pm 1.57***
Hb, g/L	106 (93–117)	109 (95–117)	103 (92–117)	109 (95–117)
CRP, mg/L	89 (38–161)	26 (8–45) ***	106.5 (65–192.5)	44 (18–119) ***
NT-proBNP, pg/mL	9795 (4074–31 641)	3569 (2083–19 792) **	5753 (2998–22 335)	27 944 (7372–40 711) **
Ferritin, ug/L	1208 (731–2400)	617 (389–937) ***	1459 (933–2708)	857 (573–1885.5) **
25VitD, nmol/L	68 (42–98)	80 (49–102)	71 (46–103)	75 (46–101)
Cholecalciferol, IU/week	20 000 (18 500–20 000)	20 000 (20 000–20 000)	20 000 (0–20 000)	20 000 (14 000–20 000)
Alfacalcidol, ug/week	0 (0–3.0)	0 (0–3.0)	0 (0–0)	0 (0–3.5)***
Current immunosuppression	11 (5.5%)	8 (5.0%)	3 (4.1%)	16 (5.5%)
Historic immunosuppression	37 (18.4%)	39 (24.2%)	10 (13.7%)	66 (22.8%)*

Note: To allow analysis of the effect of age, the Charlson comorbidity score has been calculated without the age factor.

* $p < .05$, ** $p < .01$, *** $p < .001$ inpatients versus outpatient and died versus survived.

TABLE 4 Univariate and multivariate factors associated with patients tested positive for COVID 19. Odds ratio (OR), 95% confidence intervals (95% CI). If required nonparametric variables were log-transformed to improve variable distribution. Peritoneal dialysis (PD), haemodialysis (HD), immunosuppressive medications (immune Rx), 25 OH vitamin D (25VitD), nmol/L; haemoglobin (Hb), g/L; C reactive protein (CRP), mg/L; N-terminal probrain natriuretic peptide (NT-proBNP), pg/L; ferritin, ug/L. Charlson comorbidity and clinical frailty scores odds ratio per point

	Univariate		Multivariate	
	Crude OR (95% CI)	<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
Age	1 (0.99, 1.01)	.937		
Female versus male	0.99 (0.76, 1.29)	.968		
HD versus PD	3.41 (2.24, 5.19)	<.001	5.78 (3.6, 9.3)	<.001
Charlson comorbidity	1.07 (1, 1.15)	.046	1.05 (0.96, 1.16)	.266
Frailty score	1.14 (1.03, 1.25)	.008	1.06 (0.94, 1.19)	.374
Current immunosuppression	0.99 (0.56, 1.76)	.982		
Cholecalciferol dose, IU/week	1.0 (1.0, 1.2)	<.001	1.01 (1.01, 1.2)	<.001
Alfacalcidol dose, ug/week	0.9 (0.86, 0.94)	<.001	0.88 (0.84, 0.93)	<.001
Log 25VitD	0.82 (0.68, 1)	.047	0.83 (0.67, 1.03)	.086
Log Hb	0.22 (0.09, 0.55)	.001	0.31 (0.1, 0.95)	.041
Log CRP	1.07 (0.98, 1.18)	.143		
Log NT-proBNP	1.03 (0.94, 1.13)	.587		
Log ferritin	0.96 (0.83, 1.12)	.635		

Note: To allow analysis of the effect of age, the Charlson comorbidity score has been calculated without the age factor.

patients tested positive for COVID-19, and vitamin D levels were not statistically different (male 57 (46–97) versus female 67 (65–81.8) nmol/L), or those admitted to hospital (male 50.5 (29.3–93.8) versus female 54(41.5–80.5) nmol/L).

We then compared the demographics of patients with COVID-19 who were more severely ill and required acute hospital in-patient admission with those who did not require hospital admission, and were managed at home, as out-patients (Table 3). Patients admitted

TABLE 5 Univariate and multivariate factors associated with patients who tested positive for COVID 19 and required hospital admission compared to those patients who were managed as outpatients. Odds ratio (OR), 95% confidence intervals (95% CI). If required nonparametric variables were log-transformed to improve distribution. Peritoneal dialysis (PD), haemodialysis (HD), current immunosuppressive medications (immune Rx), 25 OH vitamin D (25VitD), nmol/L; haemoglobin (Hb), g/L; C reactive protein (CRP), mg/L; N-terminal probrain natriuretic peptide (NT-proBNP), pg/L; ferritin, ug/L. Odds ratio for log transformed variables per log unit

	Univariate		Multivariate	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age year	1.03 (1.02, 1.05)	<.001	1.16 (1, 1.36)	.058
Gender				
Male	Reference	1		
Female	0.72 (0.47, 1.09)	.122		
Modality				
PD	Reference	1		
HD	4.23 (1.58, 11.36)	.004		
Charlson comorbidity	1.19 (1.05, 1.34)	.005	7.36 (1.28, 42.19)	.025
Frailty score	1.24 (1.08, 1.43)	.002	0.83 (0.5, 1.35)	.449
Current immunosuppression	0.88 (0.45, 1.73)	.72		
Cholecalciferol dose	1.0 (1.0, 1.0)	.014	1 (1.0, 1.0)	.915
alfacalcidol dose	0.96 (0.92, 1.01)	.149		
Log 25VitD	0.8 (0.58, 1.11)	.182		
Log Hb	0.45 (0.1, 2.03)	.298		
Log CRP	2.06 (1.65, 2.56)	<.001	2.37 (1.43, 3.92)	.001
Log NT-proBNP	1.3 (1.01, 1.68)	.046	1.9 (1.14, 3.16)	.014
Log ferritin	2.48 (1.62, 3.8)	<.001	1.88 (0.88, 4)	.101

Note: To allow analyse the effect of age, the Charlson comorbidity score has been calculated without the age factor.

to hospital were older, with greater comorbidity and frailty scores, higher serum CRP, NT-proBNP and ferritin, and were prescribed similar doses of both cholecalciferol and alfacalcidol. Patients who died and had tested positive for COVID-19 were again older, with greater comorbidity and frailty scores, and higher median serum CRP, and ferritin, but had been prescribed lower dosages of alfacalcidol. Survival of patients who tested positive for COVID-19 was not affected by current prescription of immunosuppressants, however survival was greater for those who had received immunosuppressants in the past (Table 3).

On univariate analysis greater frailty and comorbidity scores and HD modality were associated with COVID-19 positivity, along with lower serum 25 vitamin D levels despite prescription of higher doses of cholecalciferol, and prescription of lower doses of alfacalcidol and lower haemoglobin (Table 4). However, on multivariable testing only HD, lower haemoglobin and greater cholecalciferol dosing remained associated with contracting COVID-19.

We then compared disease severity and on univariate analysis, and illness requiring admission to hospital with COVID-19 was associated with increasing age, frailty and comorbidity scores and HD modality, along with higher serum CRP, ferritin and NT-proBNP, along with greater prescribed cholecalciferol dosages (Table 5). Whereas, on multivariable testing only comorbidity, CRP and NT-proBNP were associated with disease severity requiring hospital admission.

4 | DISCUSSION

Vitamin D plays a key role in the innate immune system through the production of antimicrobial peptides, including cathelicidin. As such, vitamin D could potentially have an important regulatory function in reducing the risk of respiratory tract, skin and gastrointestinal infections,¹⁴ and vitamin D deficiency has been reported to increase the risk of some respiratory infections, including tuberculosis.¹⁵ We therefore reviewed the prescription of 25 hydroxylated vitamin D (cholecalciferol), one hydroxylated vitamin D (alfacalcidol) and serum 25 hydroxylated vitamin D (25VitD) concentration in our dialysis population and their association with susceptibility to COVID 19 infections.

Almost 35% of our dialysis population of just over 1000 patients tested positive for COVID-19. The majority of patients testing positive were in-centre HD patients; 38.9% of the HD patients compared to 16.8% of PD patients, demonstrating the difference in the risk of contracting a respiratory virus when attending in-centre dialysis centres compared to PD, a home-based therapy. This increased risk COVID-19 infection for HD patients is in keeping with previous reports of an increased risk of other respiratory tract infections in HD patients compared to PD patients.¹⁶ Patients contracting COVID-19 had greater comorbidity and frailty, with lower haemoglobin and serum albumin. More frail patients were less able to independently travel to and from dialysis centres, thus more reliant on communal

transport and further increasing their risk of exposure. There were no significant differences in the number of patients contracting COVID-19 and those remaining COVID-19 free by current prescription of steroids and other immunosuppressants, whilst slightly fewer COVID-19 patients had been historically treated with immunosuppressants. Although our centre policy is to prescribe cholecalciferol to all dialysis patients with a 25Vit D of <50 nmol/L, 25VitD concentrations were lower in those patients who tested positive for COVID-19, and proportionally more patients with inadequate levels of 25VitD contracted COVID-19.

Previous reports have suggested that patients with low 25VitD levels are at increased risk of contracting viral and bacterial respiratory tract infections.¹⁷⁻¹⁹ As part of the UK government response to the first COVID-19 pandemic wave, Public Health England (PHE), the National Institute for Clinical Excellence (NICE), and the Scientific Advisory Committee on Nutrition (SACN) issued joint guidelines advising all UK adults to take a 25Vit D supplement of 10 ug/day.²⁰

Low 25VitD levels have been reported from patients with a variety of chronic diseases.²¹ Our centre policy was to administer cholecalciferol to HD patients by the dialysis staff, to ensure compliance. Even so, prescribing a single weekly dose of 20 000 IU cholecalciferol did not result in achieving adequate levels in a substantial number of patients. This would suggest that 25VitD levels should be monitored and dosages of cholecalciferol titrated accordingly.

In dialysis patients, prescribing 25VitD supplementation may not necessarily result in adequate 1,25 dihydroxylated vitamin D levels. Thus, we also compared alfacalcidol prescribing, and patients contracting COVID-19 had lower alfacalcidol dosing. Although not all prescribed medicines may always be taken by patients, as with cholecalciferol, alfacalcidol was administered by dialysis staff to HD patients in the dialysis centres, so ensuring compliance, whereas PD patients were prescribed medicines to be taken at home. Thus, on multivariable testing lower prescription of weekly alfacalcidol dosages were associated with contracting COVID-19, whereas higher doses of cholecalciferol were also associated with COVID-19 infection. One interpretation of this apparent paradox of alfacalcidol and cholecalciferol dosing on susceptibility to COVID-19 is that higher doses of cholecalciferol had been prescribed in response to lower 25VitD levels. This raises the possibility that the lower prescription of alfacalcidol, and lower 25VitD levels leads to reduced 1,25 dihydroxylated vitamin D, and so predisposed dialysis patients to COVID 19 infection, so supporting other studies reporting an increased risk of respiratory tract infections in patients with reduced 25VitD levels.²¹

Previous publications have suggested that 25VitD deficiency may not only predispose to susceptibility and increased frequency of respiratory tract infections, but also be associated with greater disease severity and mortality.²² As for COVID-19 there are a number of recent reports suggesting that low levels of 25VitD are also associated with more severe COVID-19 infection and mortality.²³⁻²⁵ However, reviewing our data patients with more severe disease requiring hospital admission, these patients were older, with greater underlying comorbidity and frailty, and higher concentrations of markers of disease activity; CRP, ferritin, and NT-proBNP, in keeping with other

studies in nondialysis and dialysis patients.²⁶⁻²⁹ We found that patients requiring acute hospital admission had marginally lower, but not significantly lower 25VitD levels, but had received similar dosages of alfacalcidol, but alfacalcidol dosages were lower in those who died with COVID-19. However, on multivariate testing only comorbidity, and markers of inflammation; CRP and NT-proBNP remained significantly associated with disease severity requiring hospital admission, similar to observational reports from nondialysis patients.²⁶⁻²⁸

Previous reports have highlighted an association between 25VitD deficiency and contracting COVID-19.¹⁸ As 25VitD has to be converted through to 1,25 (OH)₂D₃ to activate the vitamin D receptor on immune cells, then normal serum 25VitD levels in patients with chronic kidney disease patients may not necessarily translate into therapeutic levels of 1,25 (OH)₂D₃. Although we were unable to directly measure 1,25 (OH)₂D₃, our retrospective analysis from just over 1000 dialysis patients showed that those patients who contracted COVID-19 had lower levels of 25VitD, despite greater prescription of cholecalciferol, and were prescribed lower doses of alfacalcidol, suggesting that lower levels of active vitamin D may predispose to an increased risk for infection with COVID-19.³⁰ However, compared to previous reports from nondialysis patients admitted to hospital, we were unable to demonstrate any association between 25VitD levels and prescription of cholecalciferol with disease severity or mortality.²²⁻²⁴ This may have been due to our study having enrolled only patients with kidney failure, and in such patients serum 25VitD levels may not necessarily correlate with those of 1,25 dihydroxylated vitamin D.

On the other hand, although cholecalciferol is readily absorbed from the small intestine, and its metabolites are excreted primarily in the bile and faeces, cholecalciferol is 50% to 80% protein bound, by vitamin D-binding protein (VDP). As such the lower 25VitD levels measured may reflect lower concentrations of VDP, and overall our patients who contracted COVID-19 had lower serum albumin, along with lower haemoglobin, and greater pro-BNP.³¹ However, the difference in median serum 25VitD concentrations was only noted for PD and not for the HD patients, and other markers of inflammation, including CRP and ferritin were not significantly different. Albumin levels are typically lower in PD patients due to increased capillary permeability and dilution.^{32,33}

As with any observational study we can only report associations, and not causality. Due to cholecalciferol and alfacalcidol prescription we did not have patients with very low levels of 25VitD, as reported in other series of general medical patients, although measurements in these other studies were taken during hospital admission.²²⁻²⁴ As such, this may have obscured any potential effect of vitamin D on disease severity. Although it is most likely that the greater prescription of cholecalciferol by clinicians was in response to lower 25VitD levels, it has to be accepted that there may be many other causes of lower 25VitD levels, including inadequate sun-light exposure to lower VDP. Compared to the general population, conversion of 25VitD to 1,25 dihydroxy vitamin D is impaired in patients with end-stage kidney disease, and it is the active form of vitamin D which stimulates the innate immune response. To overcome this, our kidney dialysis patients were

prescribed alfacalcidol to control chronic kidney disease mineral bone disease (CKD-MBD). Prescription of alfacalcidol was lower in those patients who tested positive for COVID-19, both for the HD and PD patients. Centre policy for the prescription of alfacalcidol was to follow the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, aiming to primarily control parathyroid hormone (PTH), serum calcium, and phosphate.³⁴ Although PTH secretion can be suppressed in patients with acute sepsis, studies have not shown any association with frailty,³⁵ and it is therefore unlikely that the difference in prescription can be attributed to frailty or comorbidity. The slightly lower prescription of alfacalcidol in the PD patients probably reflects usage of higher calcium concentrations in the peritoneal dialysis fluids compared to the haemodialysis dialysates.

The strength of our study is that we routinely measured 25VitD in our patients, and as such we reported on prehospitalisation 25VitD concentrations, whereas previous studies measured 25VitD at the time of hospitalisation,²²⁻²⁴ and critical illness is recognized to lower albumin and VDP and so reducing total serum 25VitD concentrations.³⁶ Thus, this acute phase response to inflammation may confound the results of some studies, although we noted that those patients who died due to COVID-19 infection were observed to have been prescribed lower dosages of alfacalcidol. As with other studies, disease severity and outcomes were more influenced by underlying age, comorbidity and the severity of the inflammatory response.²⁶⁻²⁹ Only a small minority of our patients were admitted to intensive care, and although there were a number of clinical trials for potential treatments for COVID-19, dialysis patients were excluded from the initial trials. Similarly, the vaccination programme for our dialysis patients only started in late February 2021, and although there were some differences noted between the responses to AZD1222 and BNT162B2, both vaccines led to a much lower neutralising antibody response for dialysis patients after a single dose.³⁷ Greater vitamin D status has been reported to improve the seroconversion response to influenza vaccinations, and two clinical studies have suggested potential benefits of vitamin D supplementation in improving the immunological response to COVID-19 vaccines.³⁸ Vitamin D potentiates the production of TH α β cytokines, which both activate CD8+ T lymphocytes to attack virus infected cells and increase the differentiation of B cells to produce neutralising antibodies to COVID-19. Further study is required to determine whether this equally applies to dialysis patients.

In this large cohort of dialysis patients, those who tested positive for COVID-19 had lower 25VitD levels, and more had subtherapeutic 25VitD levels. Suggesting that vitamin D status had an effect on the susceptibility to contract COVID-19 infection. Although centre practise was to provide 25VitD supplementation, many patients did not achieve therapeutic levels, implying that monitoring and dose titration is necessary. In addition, we found that patients contracting COVID-19 were prescribed lower doses of alfacalcidol compared to those who did not contract COVID-19. Although patients with lower levels of vitamin D appeared to have a greater risk for contracting COVID-19, on multivariable testing other factors, including underlying patient comorbidity and markers of disease inflammation had a greater effect on patient outcomes than vitamin D status alone.

AUTHOR CONTRIBUTIONS

Conceptualisation: Andrew Davenport. *Data Curation:* Theerasak Tangwonglert and Andrew Davenport. *Statistical analysis:* Theerasak Tangwonglert. *Validation:* Theerasak Tangwonglert. *1st draft:* Andrew Davenport. *Revisions:* Andrew Davenport and Theerasak Tangwonglert. *Final manuscript:* Andrew Davenport and Theerasak Tangwonglert. Data R drive UCL. Ethics committee 20/SW/0077.

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CONFLICT OF INTEREST

Neither author has any conflicts of interest.

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