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An investigation into the correlation of vitamin D status and management outcomes in patients with severe COVID-19 at a South African tertiary hospital ☆

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ABSTRACT

Background: Severe coronavirus disease 2019 (COVID-19) has a poor prognosis, and biomarkers may predict disease severity. The aim of this study was to assess the effect of baseline vitamin D (VitD) inadequacy on the outcomes of patients with severe COVID-19 admitted to the intensive care unit (ICU) of a tertiary hospital in South Africa.

Methods: Patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were recruited during wave II of the pandemic in Cape Town. Eighty-six patients were included in the study. They were categorized into three groups: VitD deficient, VitD insufficient, and VitD sufficient. The VitD deficient and VitD insufficient groups were combined to form a 'VitD inadequate' group. Cox regression analysis was done to assess the association between VitD status and mortality. Factors with $P < 0.05$ in the adjusted multivariable Cox regression analysis were considered statistically significant.

Results: The proportion of VitD inadequacy was 64% (55/86); this group had a significantly higher proportion with hypertension (66%; $P = 0.012$). The Kaplan–Meier curve showed no significant difference in the probability of survival among the COVID-19 patients admitted to the ICU with or without VitD inadequacy. However, patients with elevated serum creatinine were significantly more at risk of dying (adjusted hazard ratio 1.008, 95% confidence interval 1.002–1.030; $P = 0.017$).

Conclusions: This study found a high prevalence of VitD inadequacy (combined deficiency and insufficiency) in COVID-19 patients admitted to the ICU. This may indicate a possible risk of severe disease. Whilst there was no statistically significant relationship between VitD status and mortality in this cohort, baseline VitD may be an important prognostic biomarker in COVID-19 patients admitted to the ICU, particularly in those with comorbidities that predispose to VitD deficiency.

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1. Introduction

Coronavirus disease 2019 (COVID-19) spread rapidly across the world, leading to a global pandemic, and the early waves had a very high mortality rate among severe cases. As of May 14, 2023, a total of 766 million confirmed cases of COVID-19 globally, including 6.9 million deaths, had been reported to the World Health Organization (WHO) [1]. Patients with severe COVID-19 developed what has now been termed a 'cytokine storm' associated with severe acute respiratory syndrome (SARS) and multi-organ failure [2]. This cytokine storm, a hyper-inflammatory syndrome driven by activation of the immune system, is associated with the production of very high levels of pro-inflammatory cytokines and other inflammatory markers, which are released into the systemic circulation [3,4].

Vitamin D (VitD) is known to influence immune system regulatory function [5,6]. Most of the circulating VitD (90%) is produced by cutaneous conversion of 7-dehydrocholesterol by ultraviolet light to form the precursor, VitD3, and the rest is obtained from the diet (VitD2); the two forms are hydroxylated in the liver to form 25-hydroxy VitD3 and VitD2, respectively [7]. The active form of the vitamin is synthesized by a second hydroxylation in the kidney by the 1-alpha hydroxylase enzyme to form the active metabolite $1,25(OH)_2D$ (1,25-dihydroxyvitamin D, or calcitriol) [8]. This enzyme is also present in immune cells such as macrophages and monocytes, where its activity is under the control of cytokines including interleukin (IL)-1, IL-2, and IL-15, tumour necrosis factor alpha, and interferon-gamma [9]. The downstream effect of VitD is the upregulation of genes required for the synthesis of substances such as defensins and cathelicidin, involved in immune function [10–13].

The significant role of active VitD as a selective immunosuppressant is illustrated by its ability to either prevent or markedly suppress animal models of autoimmune disease [10]. Other studies have found that VitD can also prevent or markedly suppress autoimmune encephalomyelitis, Guillain–Barré syndrome, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, and inflammatory bowel disease [14,15]. It has therefore been postulated that this may also be the case in severe COVID-19, where the marked cytokine inflammatory reaction may be dampened by VitD [16].

In South Africa, healthy adults are reportedly VitD-sufficient; however, the majority of those aged above 65 years are deficient [17]. In this population, VitD deficiency and insufficiency were found to be present in 27% and 38%, respectively [17]. It is unclear how VitD deficiency and insufficiency affect COVID-19 outcomes in the intensive care unit (ICU). The aim of this study was to assess the effect of VitD deficiency and insufficiency on patients with severe COVID-19 admitted to the ICU in a South African tertiary hospital.

2. Materials and methods

2.1. Study population

This was a prospective cohort study of patients admitted to the ICU at Tygerberg Hospital during the second COVID-19 wave from October 29, 2020 to February 10, 2021. A total of 86 patients were followed up until a definitive outcome of either death or discharged alive from the ICU to a step-down ward was established. These patients had confirmed COVID-19 by polymerase chain reaction (PCR) assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The study only included adults (≥18 years). ICU admission was based on disease severity and the availability of critical care resources. Figure 1 shows the process followed to obtain the final cohort for VitD testing.

2.2. Study setting

Tygerberg Hospital is a 1380-bed tertiary care hospital, located in the northern suburbs of the Cape Town metropole, Western Cape, in South Africa. The hospital serves a community of approximately 3.6 million from the public health system and is the main teaching hospital for Stellenbosch University Faculty of Medicine and Health Sciences.

2.3. Data collection

Clinical and demographic data was collected prospectively from the inpatient medical records. Due to COVID-19 restrictions and to limit disease spread, pictures of patient file notes were obtained at admission for detailed perusal and data capturing, outside of the wards. This was achieved by the transfer of hand-written notes into the REDCap electronic database through pictures of the files, which contained all clinical information and ICU admission notes. Laboratory data was obtained from the hospital laboratory information system (TrakCare Lab Enterprise). The laboratory service at Tygerberg Hospital is provided by the National Health Laboratory Service (NHLS), which serves all public hospitals in South Africa. Validity and quality checking of the data was performed by the supervisor of the data entry process. The VitD status of participants was categorized as follows: VitD deficiency when <30 nmol/l (<20 ng/ml), VitD insufficiency when between 31 nmol/l and 50 nmol/l (12–20 ng/ml), and VitD sufficiency if above 50 nmol/l (20 ng/ml), in accordance with the Endocrine Society guidelines [18]. Body mass index (BMI) could not be assessed due to difficulties in accurately measuring the weight and height of critically ill patients in a hospital bed.

2.4. Laboratory analyses

Serum and whole blood samples were obtained on admission to the ICU for each patient. The serum tubes were centrifuged after they were adequately clotted, and 1 ml was aliquoted into cryotubes and stored at −80°C until analysis could be performed. The tubes and storage places were marked with unique patient identification numbers for easy retrieval. Tests requiring whole blood were performed immediately on the admission samples. The following biochemical laboratory tests were performed: urea, creatinine, calcium (Ca^{2+}), phosphate (P), magnesium (Mg^{2+}), VitD, HbA1c, troponin T (TropT), and N-terminal pro-brain natriuretic peptide (NT-proBNP).

D-dimer was performed immediately after collection of the samples on whole blood, using the Sysmex CS-2000i system (Sysmex Medical Electronics, Germany). VitD levels were determined using a Roche Cobas 6000 Elecsys II total VitD assay (Roche Diagnostics, Mannheim, Germany). This assay uses the electrochemiluminescent method to detect both VitD2 and VitD3. The analytical methods used for the other biochemistry tests have been described in an earlier study [19]. The estimated glomerular filtration rate (eGFR) was obtained with all serum creatinine results from the laboratory, and was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without a correction for race, as recommended in a local study [20]. Strict internal quality control procedures were followed, and the NHLS laboratory participates in external quality assurance schemes, is accredited by the South African Accreditation Service (SANAS), and complies with ISO15189 regulations.

2.5. Ethics

Research approval was obtained from the Health Research Ethics Committee of Stellenbosch University (approval number N20/04/002_COVID-19). A waiver of consent was obtained from the Ethics Committee due to the expedited nature of this study. The research project was conducted according to the ethical principles of the Declaration of Helsinki. Patient data was anonymized to protect their privacy and adhere to the Protection of Personal Information Act of South Africa [21].

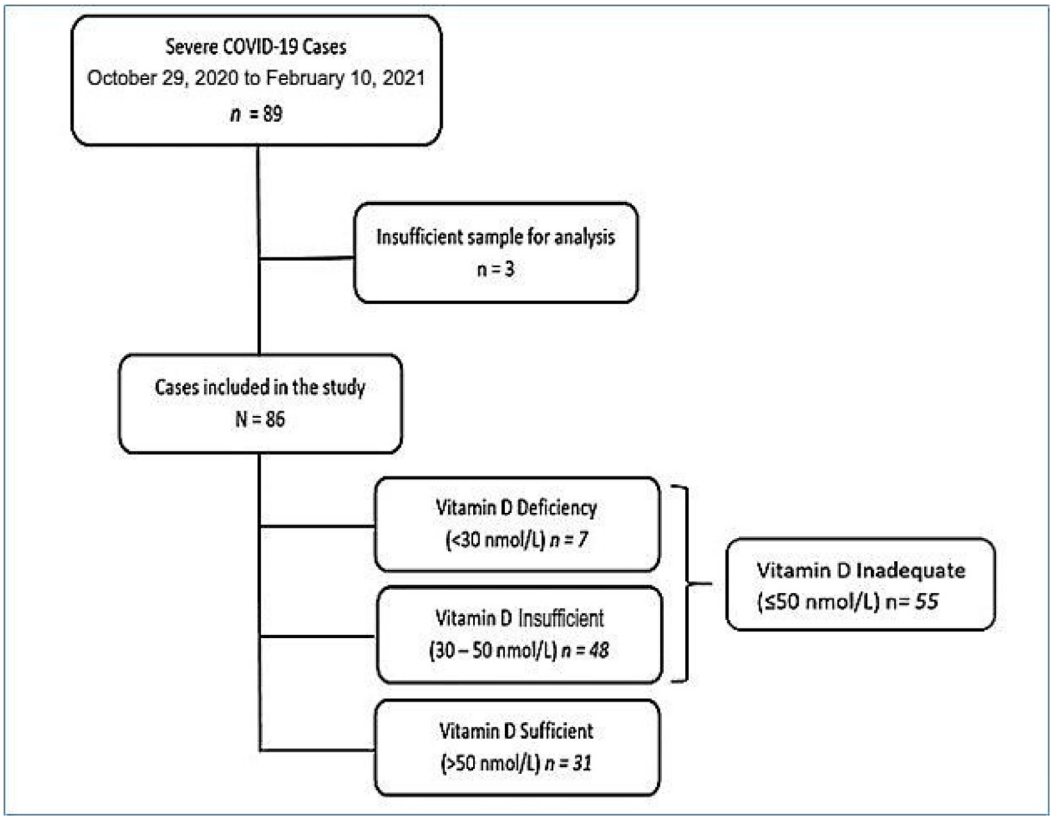

Figure 1. Study flow chart.

2.6. Outcomes and predictor variables

The main outcome of interest was mortality while in the ICU, with VitD as the main exposure. The patients were categorized into three groups: VitD deficient (<30 nmol/l), insufficient (30–50 nmol/l), and sufficient (>50 nmol/l). As only 8% of cases were VitD deficient, this group was combined with the insufficient group to form a group called 'VitD inadequate' (<50 nmol/l). Comparative analyses were undertaken between the VitD inadequate and the VitD sufficient groups to assess differences and similarities in relation to mortality among the patients admitted to the ICU. Patients were stratified by VitD status and the proportion of those who died in the ICU. The clinical variables studied included the need for respiratory support and mortality stratified by VitD status.

Previous medical history was documented, including comorbidities such as hypertension, diabetes mellitus, and dyslipidaemia, and smoking status.

2.7. Statistical analyses

Continuous variables were expressed as the median with interquartile range, since the data was non-normally distributed. Categorical variables were expressed using frequencies and percentages. The Chi-square test or Fisher's exact test was used to assess the association between VitD status and the categorical variables. The median test was used to assess the equality of the median of the continuous variables between the VitD status groups. Schoenfeld residuals and the Cox proportional hazards test were used to assess the proportional hazards assumption. Cox regression was used to assess significant associations between demographic data, VitD status, and mortality. Factors associated with mortality and VitD status at $P < 0.05$ in the unadjusted univariable Cox regression were included in a multivariable model to identify predictor variables associated with VitD status and mortality. Adjusted hazard ratios (AHR) and their 95% confidence intervals (CI) were used as a measure of association. All statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA) and R version 4.1.0 (R Core Team) with R Studio version 1.4.1 (R Studio Team) statistical software.

3. Results

Of the total 86 patients included in the study and grouped by their VitD status, 71% were female ($n = 61$) and 29% were male ($n = 25$). Because of the skewed sex distribution, both the inadequate and sufficient groups were dominated by female patients at 69% and 74%, respectively.

Most patients in the inadequate group had diabetes (53%, $n = 25$; $P = 0.670$) and hypertension (66%, $n = 31$, $P = 0.012$). Patients with VitD inadequacy had a higher death rate compared to those in the sufficient group, 64% and 59%, respectively (Table 1).

Both groups had elevated inflammatory markers such as C-reactive protein (CRP) and ferritin. The ferritin levels were, however, lower in the inadequate group, although still above the reference range. The rest of the biochemical markers did not show any differences between the two groups (Table 2). Factors that were found to have an association with VitD levels and mortality included sex and creatinine, with an unadjusted hazard ratio (HR) of 1.66 (95% CI 1.00–2.75) for sex ($P = 0.050$) and 1.008 (95% CI 1.002–1.03) for serum creatinine ($P = 0.017$) (Table 3).

A slightly lower proportion of those with VitD inadequacy required invasive ventilation, while the sufficient group had a slightly higher proportion of patients requiring invasive ventilation (41% vs 38%).

Patients in the inadequacy group had a higher mortality (64%) as compared to those in the sufficient group (59%). The survival curve

Table 1
Socio-demographic information and biochemical profiles according to vitamin D status

Characteristic	Total (N = 86)	Vitamin D categories		P-value
		≤50 nmol (n = 55)	>50 nmol (n = 31)	
Age at admission (years), median (IQR)	54.33 (46.10–62.00)	55.99 (47.20–63.00)	53.00 (39.89–60.13)	0.093
Sex				0.660
Female	61 (71%)	41 (69%)	20 (74%)	
Male	25 (29%)	18 (31%)	7 (26%)	
Hypertension				0.012*
Yes	38 (56%)	31 (66%)	7 (33%)	
No	30 (44%)	16 (34%)	14 (67%)	
Hyperlipidaemia				0.640
Yes	5 (7%)	3 (6%)	2 (10%)	
No	63 (93%)	44 (94%)	19 (90%)	
Diabetes				0.670
Yes	35 (51%)	25 (53%)	10 (48%)	
No	33 (49%)	22 (47%)	11 (52%)	
Death/discharge				0.650
Discharge	32 (37%)	21 (36%)	11 (41%)	
Death	54 (63%)	38 (64%)	16 (59%)	
Ventilation				0.772
Non-invasive	49 (57%)	32 (62%)	16 (59%)	
Invasive	37 (43%)	20 (38%)	11 (41%)	

IQR, interquartile range.
* $P < 0.05$, significant.

Table 2
Biochemical results; median (IQR) values

	Reference range	Total (N = 86)	Vitamin D categories		P-value
			≤50 nmol (n = 55)	>50 nmol (n = 31)	
D dimer (n = 71)	0.00–0.25 mg/l	0.78 (0.40–3.50)	0.77 (0.35–3.75)	0.82 (0.47–1.51)	0.970
cTropT (n = 63)	<100 ng/l	13 (6–27)	13 (7–27)	14 (5–27)	0.950
LDH (n = 34)	100–190 U/l	736 (582–900)	696 (602–891)	818 (542–980)	0.620
NT-proBNP (n = 59)	<125 ng/l	179 (88–791)	174 (105–642)	188 (68–1587)	0.950
HbA1c (n = 70)	<6.5%	7.6 (6.3–8.0)	7.60 (6.3–9.0)	7.4 (6.1–8.6)	0.540
PCT (n = 61)	<0.5 μg/l	0.31 (0.15–1.12)	0.35 (0.16–0.96)	0.30 (0.14–1.38)	0.990
Ferritin (n = 50)	13–150 μg/l	855 (469–1292)	721 (469–1088)	1055 (434–2561)	0.310
CRP (n = 77)	<10 mg/l	137 (86–221)	137 (80–224)	139 (107–221)	0.750
Ca^{2+} (n = 46)	2.12–2.59 mmol/l	2.06 (2.01–2.18)	2.05 (2.01–2.19)	2.09 (2.02–2.16)	0.960
Mg^{2+} (n = 46)	0.63–1.05 mmol/l	0.94 (0.89–1.06)	0.97 (0.89–1.07)	0.93 (0.82–1.01)	0.120
Phosphate (n = 36)	0.78–1.42 mmol/l	1.15 (0.93–1.53)	1.17 (0.91–1.57)	1.12 (1.00–1.35)	0.580
Urea (n = 79)	2.1–7.1 mmol/l	6.7 (4.9–8.6)	6.9 (5.1–8.7)	5.8 (4.4–7.9)	0.160
Creatinine (n = 79)	49–90 μmol/l	76 (66–102)	76 (65–101)	76.00 (69–106)	0.600
eGFR (n = 77)	>60 mL/min/1.73 m^2	80 (70–96)	80 (70–100)	80 (72–92)	0.760

Ca^{2+}, calcium; CRP, C-reactive protein; cTropT, cardiac troponin T; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; Mg^{2+}, magnesium; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCT, procalcitonin.

Table 3
Factors associated with mortality, vitamin D status, and demographics

Characteristic	HR (95% CI)	P-value	AHR (95% CI)	P-value
Vitamin D	1.00 (0.99–1.01)	0.932	1.001 (0.99–1.02)	0.883
Age at admission	0.99 (0.97–1.01)	0.424	0.98 (0.96–1.01)	0.159
Sex: Male	1.66 (1.00–2.75)	0.050*	1.39 (0.80–2.44)	0.245
Hypertension	1.08 (0.63–1.87)	0.779	1.19 (0.61–2.33)	0.608
Diabetes	1.13 (0.69–1.85)	0.627	1.02 (0.55–1.92)	0.932
Ventilation: Invasive	1.35 (0.85–2.17)	0.203		
D dimer	1.02 (0.98–1.08)	0.234		
NT-proBNP	1.000 (0.99–1.00)	0.667		
HbA1c	1.03 (0.95–1.11)	0.536		
Creatinine	1.006 (1.0003–1.01)	0.039*	1.008 (1.002–1.03)	0.017*
CRP	0.999 (0.996–1.00)	0.311		
Ca^{2+}	0.41 (0.04–3.84)	0.438		
eGFR	0.99 (0.98–1.00)	0.119		
Urea	1.01 (0.96–1.07)	0.602		
Mg^{2+}	0.84 (0.15–4.78)	0.846		
Ferritin	1.00 (0.99–1.0002)	0.997		
Phosphate	2.46 (1.23–4.90)	0.010*		
PCT	1.17 (0.91–1.52)	0.208		

AHR, adjusted hazard ratio; Ca^{2+}, calcium; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; Mg^{2+}, magnesium; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCT, procalcitonin.
* $P < 0.05$, significant.

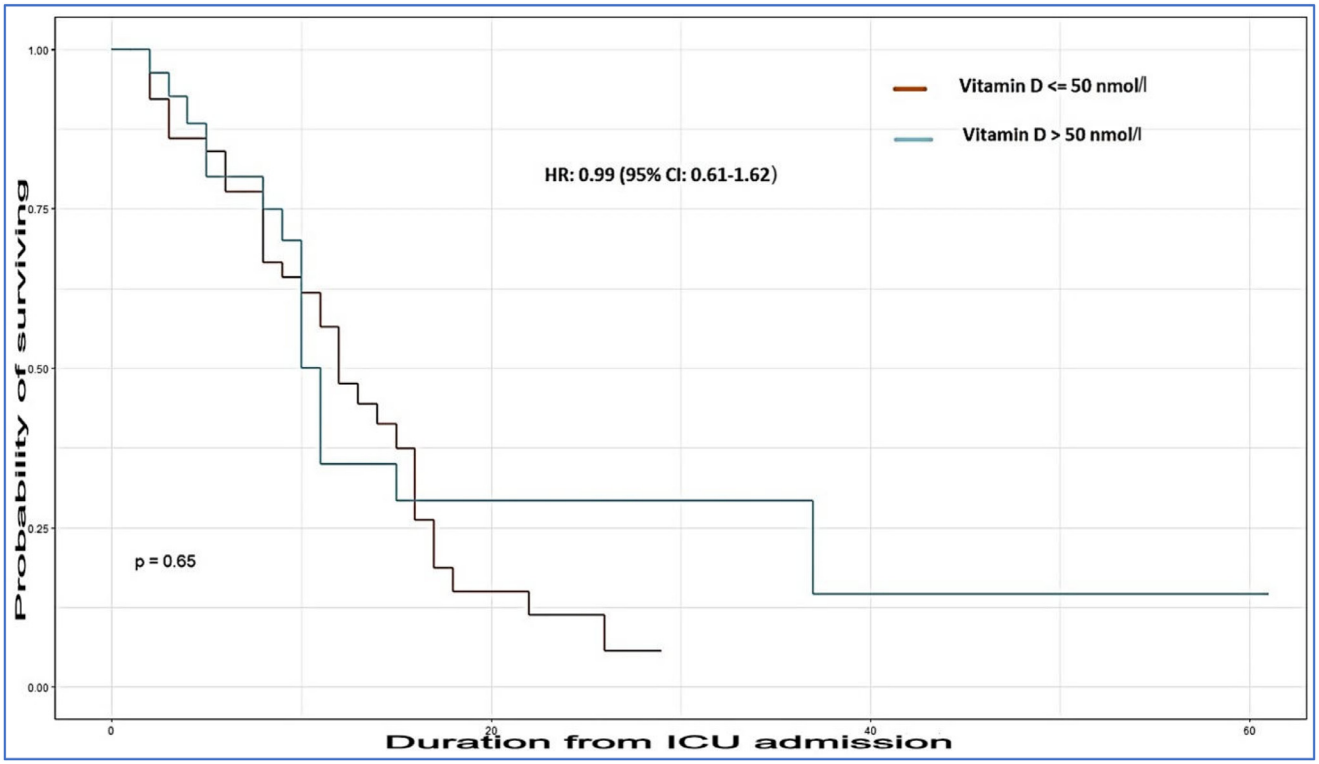

Figure 2. Probability of survival curve for COVID-19 patients admitted to the ICU, stratified by vitamin D status.

shows that there was no statistically significant difference in survival between the two groups of patients defined by their VitD levels (>50nmol/l; ≤50 nmol/l (HR 0.99 (95% CI 0.61–1.62) and $P = 0.650$ (Figure 2).

The proportional hazards assumption was tested using plots of the scaled Schoenfeld residuals of each covariate against log-time. The Schoenfeld residuals test revealed that a proportional hazard assumption had the same effect on COVID-19 patient survival rates with VitD ≤50 nmol/l and VitD >50 nmol/l ($P = 0.202$) (Figure 3).

4. Discussion

This study investigated the VitD status in a cohort of patients admitted to the ICU at Tygerberg Hospital and determined whether VitD status had any correlation with outcomes. Most patients were middle-aged and the majority were female. The main comorbidities identified were hypertension and diabetes. Most of the patients were found to have VitD inadequacy; only a very small percentage had VitD deficiency, and this group was too small to perform any further statistical analysis on. Patients with hypertension and diabetes mellitus had a higher prevalence of VitD inadequacy.

The mortality rate was higher in the group with inadequate VitD levels. However, these differences in mortality were not statistically significant. The proportion of patients requiring invasive ventilation was slightly higher in the sufficient VitD group. While this finding showed no statistical significance, physiologically, it could be explained by the presence of the cytokine storm, which causes acute respiratory distress syndrome (ARDS) and may override the modulatory effect of effectors including VitD and anti-inflammatory cytokines on the immune system [22]. In addition, it could be postulated that VitD inadequacy may have a 'protective' effect from the cytokine storm, i.e. these patients have a blunted immune response, especially in the lungs, so that even with severe disease complicated by multi-organ failure, their lung function may remain slightly preserved compared to those with adequate VitD and a hyper-inflammatory response.

No statistically significant association between VitD status and inflammatory markers, liver function, and myocardial injury markers was found. The finding of lower serum ferritin levels in the VitD inadequate group may be explained by several factors involved in immune system regulation and its role in iron storage [23]. The levels of vitamin D-binding protein (VDBP) have been reported to be low during acute inflammatory illness, making VDBP a negative acute phase reactant [24]. Some authors have further suggested that total VitD measurement is unreliable in the acutely ill patient because it will be falsely low due to the reduction of both VDBP and albumin, which transport VitD in the circulation [25]. However, other researchers have found normal or elevated VDBP levels in patients with inflammatory disorders. Aksan et al. reported a positive correlation between high sensitivity CRP and VDBP, and concluded that total serum VitD is still a reliable marker of the VitD status in this group of patients [26].

Only serum creatinine showed a statistically significant association with mortality; however, this difference was not clinically significant, as both groups had serum creatinine concentrations within the reference range. The current study VitD status findings (68% VitD inadequacy) are consistent with those of De Smet et al., who described a baseline prevalence of VitD inadequacy of 67% in patients with COVID-19, using a cut-off of 50 nmol/l [27]. A South African study found the prevalence of VitD inadequacy to be 82%, with the majority of these patients being VitD deficient at 66%, and only 8% having sufficient VitD levels. Their cohort included 100 patients with symptomatic but variable severity of COVID-19 [28]. In contrast to the South African findings from the present study and the study reported above, Teama et al. found a very high prevalence of VitD inadequacy in those with severe COVID-19 in an Ethiopian hospital [13]. Their study found a prevalence of VitD inadequacy of 97.6% and calculated a cut-off level of <45 nmol/l to be predictive of a poor prognosis, with a sensitivity of 75.9% and specificity of 60.6%. The current study cohort was slightly older at admission, with comorbidities such as hypertension and diabetes more prevalent compared to a previous study by Yoo et al. [29]. Other studies have also reported that the above comorbidities are asso-

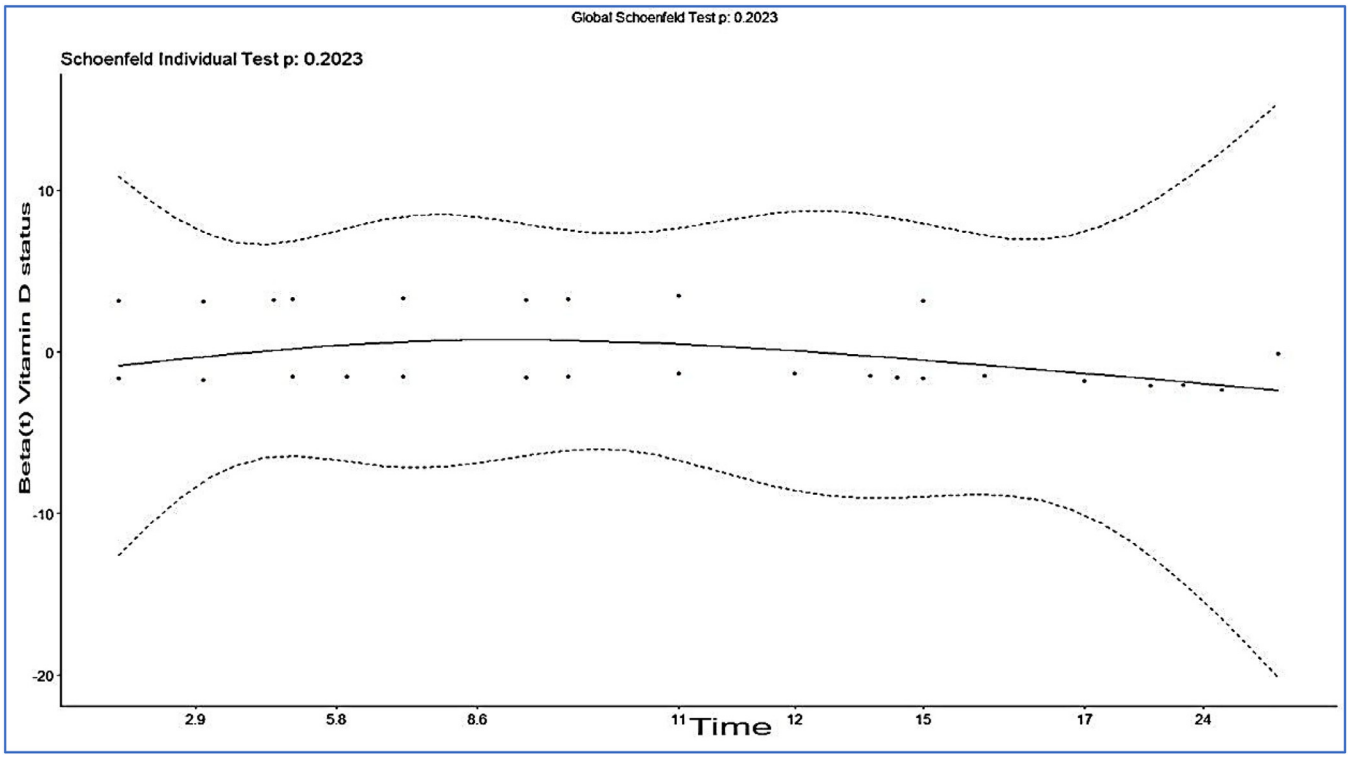

Figure 3. Assessing the proportional hazards function using Schoenfeld residuals.

ciated with VitD deficiency [30] and a higher risk of severe COVID-19 [31,32].

It is now common knowledge that the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors, leading to upregulation of the classic arm of the renin–angiotensin–aldosterone system (RAAS) pathway [33]. The effects of the classic RAAS pathway include vasoconstriction, oxidative stress, pro-inflammatory state, aldosterone release, cell proliferation, and tissue fibrosis [34]. Patients with VitD deficiency also have increased RAAS activity and angiotensin II levels, which potentially cause the aforementioned physiological changes [35]. Furthermore, VitD reduces renin expression and action against any regulatory feedback by angiotensin II, while the opposite is true in VitD deficiency, which shows an increase in renin expression [36]. The increased renin activity in VitD deficiency leads to upregulation of ACE2 activity, which in turn increases the conversion of angiotensin I to angiotensin II; the latter has been postulated to be toxic to the lungs through its action on angiotensin II type I receptors, causing severe inflammation and lung fibrosis [37]. Plasma renin is also elevated in those with hypertension and diabetes mellitus, and in most elderly patients [38]. This common thread of hyper-reninaemia between these conditions and VitD inadequacy may possibly be one of the underlying physiological mechanisms leading to the high risk of severe COVID-19 seen in patients with these comorbidities.

An association of VitD deficiency and low eGFR associated with an increased level of IL-6 as a risk of SARS-CoV-2 infection progression and a poor prognosis has been reported [39]. In addition, a low VitD level has been associated with elevated pro-inflammatory cytokines and has been demonstrated to be an independent predictor of COVID-19 severity [40]. This association was also demonstrated in an Egyptian cohort in which serum VitD was found to be inversely related to inflammatory markers such as ferritin in COVID-19 patients [41]. Other researchers have found serum VitD levels to be negatively correlated with ferritin among COVID-19 patients admitted to the ICU [13]. The current study findings of low ferritin levels in those with VitD inadequacy are unexpected and in direct contrast to this existing data. Physiologically, this could mean that in some people, VitD inadequacy predisposes to a limited immune response with less elevation of inflammatory markers such as ferritin. However, ferritin was raised above the upper limit of the reference range in both groups, and the apparent difference between the two groups did not show statistical significance.

These study results add to the growing body of observations that low VitD levels are associated with developing more severe COVID-19. Several studies have published findings and recommendations on VitD supplementation for high-risk population groups of patients with COVID-19. A recent systematic review and meta-analysis found that VitD supplementation may be beneficial for clinical outcomes of COVID-19, especially when treatment begins following the diagnosis [42]. Another systematic review showed that VitD supplementation was protective against severe COVID-19 and recommended that it can be used as an adjunct to other medical management measures [43], while a narrative review by Bae et al. concluded that VitD supplementation to maintain serum levels above 50 nmol/l can be beneficial in managing the risk and possibly mitigate the mortality associated with severe COVID-19 [44].

However, more recent clinical trials found that VitD supplementation had no effect on the risk of SARS-CoV-2 infection, disease development, or the severity thereof [45,46]. Additionally, there has been some controversy regarding the role of VitD in COVID-19 after some earlier studies were retracted due to the fast tracking of publications early in the pandemic [47,48]. In our view, even if the current data on VitD supplementation may be inconclusive, it remains important to further investigate any factors that may be protective against severe COVID-19.

South Africa has a high burden of infectious diseases, including human immunodeficiency virus (HIV) (8.23 million people) and tuberculosis (TB), with a prevalence of 737 per 100 000 population [49]. The South Africa National Institute for Communicable Diseases (NICD) has reported that TB is the leading cause of death in South Africa, accounting for 6% of all deaths; HIV is the fifth commonest cause of death in South Africa, with a co-infection rate between 28.8% and 59% [50].

Some studies have found an association between inadequate VitD status and the development of TB and other adverse outcomes [51,52]. Lung damage from previous or current TB infection may predispose these patients to ARDS and possibly respiratory failure due to the characteristic lung-centric inflammation found in severe COVID-19 [53].

HIV and antiretroviral therapy have been shown to affect VitD metabolism, mostly affecting bone health [54]; the immune system may also be affected and requires further studies to investigate. Another South African study found that VitD deficiency was as prevalent as 42–74% among HIV-infected individuals [55]. It is therefore reasonable to postulate that VitD supplementation could benefit this group of patients as well, and needs further investigation in future studies. Although we have no data on these two infectious diseases for the study cohort, it is possible that they may play a role in the course of COVID-19 disease, especially in those who are undiagnosed, with an unsuppressed viral load or low CD4 cell count that may affect their morbidity and mortality from COVID-19.

There is paucity of data on VitD status and its relationship to COVID-19 severity and outcomes from the African Continent. This study therefore creates an opportunity to further interrogate the role of VitD in viral infections with a focus on ascertaining its relationship to the severity of diseases caused by SARS-CoV-2. This study adds value due to the homogeneous nature of the patient population; all were admitted to the ICU, managed by the same group of clinicians, and all the VitD tests were performed on the same day by the same laboratory, thereby avoiding the effects of intra-laboratory variability in patient results. It appears that this is among the few studies assessing the effect of VitD on COVID-19 severity and outcomes in an African population.

There are two important limitations of this study to bear in mind. One is the small sample size of both the whole cohort and the VitD deficient group. This might have diluted the effect of VitD deficiency on the disease outcome. The second main limitation is the lack of a control group of patients with mild or moderate disease; this limited any comparison of VitD status and outcomes by disease severity. Larger, multi-centre studies in Africa are needed that would increase the power of the study to detect meaningful differences.

In conclusion, this study found a high prevalence of VitD inadequacy, i.e. a combination of deficiency and insufficiency, in COVID-19 patients admitted to the ICU during the second wave. This may have contributed to their risk of severe disease. Even though no statistically significant relationship was found between VitD status and mortality in this cohort, this study provides evidence that baseline VitD may play an important role in these patients, particularly those with comorbidities that are associated with VitD inadequacy.

Author contributions

Conceptualization: TPJ, AEZ. Study design: LNS, AY, PSN. Data collection: TPJ, VN, AEZ. Statistical analysis: LNS, AY, PNS. Drafting the manuscript: TPJ, LNS, AEZ, PSN. Reviewing the manuscript for intellectual content: MJK, TEM, RTE. Reviewing the final draft of the manuscript: TPJ, LNS, MJK, AY, VN, JLT, ZCC, BWA, CFK, EMI, UL, TEM, RTE, AZ, AEZ, PSN. All authors approved the final version of the manuscript.

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Declarations

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