ORIGINAL ARTICLE

Severe vitamin D deficiency is not related to SARS-CoV-2 infection but may increase mortality risk in hospitalized adults: a retrospective case–control study in an Arab Gulf country

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Abstract

Purpose As the world continues to cautiously navigate its way through the coronavirus disease 2019 (COVID-19) pandemic, several breakthroughs in therapies and vaccines are currently being developed and scrutinized. Consequently, alternative therapies for severe acute respiratory coronavirus 2 (SARS-CoV-2) prevention, such as vitamin D supplementation, while hypothetically promising, require substantial evidence from countries affected by COVID-19. The present retrospective case–control study aims to identify differences in vitamin D status and clinical characteristics of hospitalized patients screened for SARS-CoV-2, and determine associations of vitamin D levels with increased COVID-19 risk and mortality.

Methods A total of 222 [SARS-CoV-2 (+) $N = 150$ (97 males; 53 females); SARS-CoV-2 (−) $N = 72$ (38 males, 34 females)] out of 550 hospitalized adult patients screened for SARS-CoV-2 and admitted at King Saud University Medical City-King Khalid University Hospital (KSUMC-KKUH) in Riyadh, Saudi Arabia from May–July 2020 were included. Clinical, radio-logic and serologic data, including 25(OH)D levels were analyzed.

Results Vitamin D deficiency (25(OH)D < 50 nmol/l) was present in 75% of all patients. Serum 25(OH)D levels were signifi-cantly lower among SARS-CoV-2 (+) than SARS-CoV-2 (−) patients after adjusting for age, sex and body mass index (BMI) (35.8 ± 1.5 nmol/l vs. 42.5 ± 3.0 nmol/l; $p = 0.037$). Multivariate regression analysis revealed that significant predictors for SARS-CoV-2 include age > 60 years and pre-existing conditions ($p < 0.05$). Statistically significant predictors for mortality adjusted for covariates include male sex [Odds ratio, OR 3.3 (95% confidence interval, CI 1.2–9.2); $p = 0.02$], chronic kidney disease [OR 3.5 (95% CI 1.4–8.7); $p = 0.008$] and severe 25(OH)D deficiency (< 12.5 nmol/l), but at borderline significance [OR 4.9 (95% CI (0.9–25.8); $p = 0.06$].

Conclusion In hospital settings, 25(OH)D deficiency is not associated with SARS-CoV-2 infection, but may increase risk for mortality in severely deficient cases. Clinical trials are warranted to determine whether vitamin D status correction provides protective effects against worse COVID-19 outcomes.

Keywords Vitamin D · COVID-19 · Case–control · Saudi Arabia · Severe vitamin D deficiency

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Background

There is universal acceptance that the exponential spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel pathogen responsible for coronavirus disease 2019 (COVID-19), had instantaneously and irreversibly disrupted normalcy both at an individual level and most, if not all of the global affairs for the year 2020. At present, majority of the people with COVID-19 eventually recover, given its mild to moderate course. Interestingly, approximately 45% of infected individuals are considered 'asymptomatic' and have been deemed 'silent carriers' of the pandemic [1]. Compared to its predecessors, SARS-CoV-2 is much more contagious, but with a lower death rate (2.3%) than SARS-CoV (9.5%) and even lower than the Middle Eastern Respiratory Syndrome (MERS-CoV) coronavirus (34.4%) [2]. In all coronavirus epidemics, management has been largely supportive. Nevertheless, and in the case of COVID-19, potential therapeutics for those with severe symptoms, such as convalescent plasma [3] and remdesivir [4], have been explored with promising results. In parallel, the race to provide effective vaccines are also being expeditiously developed for COVID-19 prevention [5], with the one from Pfizer® currently gaining attraction for mass production after a series of successful clinical trials [6]. Among the roster of potential therapies, one alternative treatment that has been widely accepted and in fact, included in the rapid COVID-19 management is the use of vitamin D, largely driven by empirical evidence on the association of vitamin D to viral infections [7, 8].

Vitamin D is a secosteroid pro-hormone with a well-established role in maintaining calcium homeostasis. More recently, vitamin D has gained prominence for its pleiotropic and extra-skeletal effects [9]. It is estimated that globally, more than a billion people have vitamin D deficiency, with the highest prevalence mostly coming from countries in the Middle East, including Saudi Arabia [10, 11]. Currently, vitamin D has established potency against several viral respiratory infections and has consistently been observed to accelerate healing of injured tissues, primarily the lungs [12], considered compelling reasons why vitamin D merits further exploration in its preventive role in COVID-19. Furthermore, accumulating evidence from retrospective studies done mostly in Europe [13, 14], USA [15] and China [16] indicate that lower vitamin D levels were commonly observed among hospitalized patients with confirmed COVID-19, and may have some role in determining the severity and outcome of COVID-19. To date, only two studies have been conducted in the Middle East to examine the association between vitamin D levels and risk of acquiring, and dying from, COVID-19. One large-scale study in Israel has reported vitamin D deficiency as an independent risk factor of COVID-19 infection in the general population [17]; and the retrospective study in Iran which reported that low vitamin D levels are associated with severe lung damage and higher mortality among hospitalized COVID-19 patients [18]. So far, no published studies have examined the link between vitamin D deficiency and risk of COVID-19 infection or mortality in Saudi Arabia or any Arabian Gulf countries. Data from this part of the world, which is notoriously underrepresented in medical literature, are of clinical value, given its geographic and ethnic differences as compared to other regions. In addition, the high prevalence of vitamin D deficiency in this homogenous population may offer a unique insight into the link between vitamin D levels and COVID-19 that is unique from that reported in other parts of the world.

To fill this gap, the present retrospective, case–control study aims to examine the association between vitamin D levels and clinical profiles of hospitalized individuals screened for SARS-CoV-2, and whether low vitamin D levels are associated with increased risk of COVID-19 infection and mortality in this subpopulation.

Methods

Study design and participants

In this single-center retrospective study conducted from May to July, 2020, medical records of 550 adult residents of Riyadh, KSA, who were swabbed for SARS-CoV-2 [$N = 439$ SARS-CoV-2 (+) and $N = 111$ SARS-CoV-2 (−)] and consequently admitted at KSUMC-KKUH from May–July 2020, were included [19]. Children and pregnant women were excluded.

SARS-CoV-2 screening

Diagnosis of SARS-CoV-2 infection was based on national guidelines [20]. Swab samples were obtained from the patient's nasopharyngeal and oropharyngeal orifice/s and sent to the Biosafety Level 2-facility (BSL-2) with Biological Safety Cabinet Class II (BSC-II) in KSUMC, Riyadh, KSA, following universal precautions, for reverse transcription polymerase chain reaction (RT-PCR) analysis. RNA amplification was performed using ViiA7 RT-PCR (Thermo Fisher Scientific, Waltham, MA, USA) and Altona reagents (Altona Diagnostics, Hamburg, Germany). COVID-19 Test validation was done through Chemagic™ 360-D (PerkinElmer, MA, USA). Final interpretation was based on cycle threshold (CT) values obtained from specimens using ViiA7 software. Assay specificity and sensitivity obtained were 100% based on 23 specimens. Sample investigations

were performed by certified laboratory personnel following manufacturer's recommendations for the defined cut-off cycle threshold (CT) value for each target gene.

Data collection

Clinical information included demographics (age and sex), medical history (known cases of diabetes mellitus (DM), hypertension (HPN), cardiovascular disease (CVD), congestive heart failure (CHF), chronic kidney disease (CKD), stroke as well as smoking history) and list of medications [β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers (CCB), statins, insulin, oral hypoglycemic, anticoagulants and anti-platelets] were noted on admission. Height and weight were recorded and body mass index (kg/m^2) was calculated. Obesity was defined as having a BMI ≥ 30 kg/m^2. Radiological findings, if available, were recorded.

Serological tests

Non-fasting and fasting blood samples were obtained in all admitted patients. All samples were analyzed in the KKUH-KSUMC central laboratory, a participating and accredited member of the College of American Pathologists (CAP) Laboratory Accreditation Program. Laboratory investigations included glycemic [glycated hemoglobin (HbA1c), random and fasting blood glucose (RBG and FBG, respectively)], lipids [triglycerides, low-density lipoprotein (LDL-) and high-density lipoprotein (HDL)-cholesterol] profiles of liver [alanine transferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)], renal [blood urea nitrogen (BUN) and creatinine] and inflammatory markers [ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] if available, were obtained. Serum 25(OH)D was assessed using CDC-approved vitamin D total assay kits (ADVIA Centaur®, Siemens Healthcare GmbH, Erlangen, Germany) as certified by the Vitamin D Standardization-Certification Program (VDSCP) [21], with an assay range of 9.3 to 375 nmol/l. For the purpose of this study, patients whose 25(OH)D levels were not assessed ($N=328$), were excluded. The remaining 222 patients ($N=135$ males and $N=87$ females) were included in the data analysis. A flowchart of participants is provided in Fig. 1. Vitamin D deficiency [25(OH)D < 50 nmol/l] and severe vitamin D deficiency [25(OH)D < 12.5 nmol/l] were defined based on national and regional recommendations [22, 23].
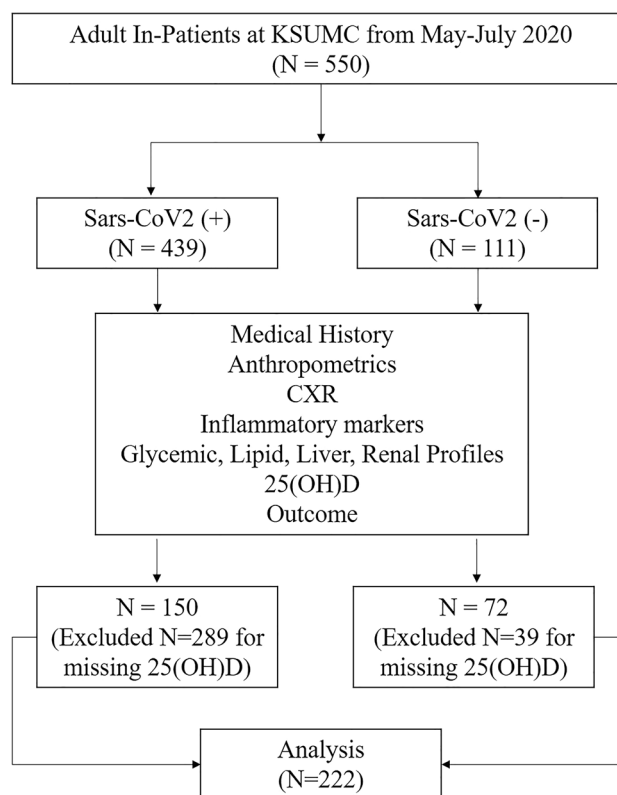

Fig. 1 Flowchart of participants

Data analysis

Data were analyzed using SPSS version 21.0 (IBM, Chicago, IL, USA). Categorical variables were presented as frequencies (N) and percentages (%). Continuous variables were presented as mean ± standard error (SE). Differences in categorical variables according to SARS-CoV-2 status were compared using Chi-Square test. Comparisons between continuous variables according to SARS-CoV-2 status were done using independent Student T test for normally distributed data and Mann–Whitney U test for non-normally distributed data. Analysis of covariance (ANCOVA) was used to obtain p values after adjusting with age, sex and BMI. Multivariate logistic regression analysis was done to determine independent predictors for outcomes of interest [death and SARS-CoV-2 (+)] using age, sex and BMI as covariates. Significance was set at $p < 0.05$.

Post hoc power analysis was done using the G*Power software [24]. While the given the sample size and obtained 25(OH)D levels between groups yield 100% power to detect significant difference, the study was underpowered to detect an association between severe 25(OH)D deficiency and COVID-19 mortality, having only 21% power (odds ratio of 1.45), given $\alpha = 0.05$.

Table 1 General characteristics of patients

Parameters	All	SARS-CoV-2 Status		p value
		Positive	Negative	
N (%)	222	150	72	
Sex (M/F)	135/87	97/53	38/34	
Age (years)	56.6 ± 16.2	55.5 ± 15.8	59.1 ± 16.8	0.12
BMI (kg/m^2)	29.6 ± 7.7	29.6 ± 6.7	29.7 ± 9.4	0.93
Nationality (%)				
Saudi	134 (60.4)	76 (50.7)	58 (80.6)	0.004
Non-Saudi	88 (39.6)	74 (49.3)	14 (19.4)	
Pre-existing conditions (%)				
Obesity	84 (37.8)	57 (38)	27 (37.5)	0.99
Hypertension	121 (54.5)	68 (45.3)	53 (73.6)	< 0.001
Diabetes mellitus	114 (47.3)	68 (45.4)	46 (63.8)	0.02
Cardiovascular disease	34 (15.3)	15 (10)	19 (26.4)	0.003
Congestive heart failure	27 (12.2)	5 (3.3)	22 (30.6)	< 0.001
Chronic kidney disease	39 (17.6)	15 (10)	24 (33.3)	< 0.001
Stroke	19 (8.6)	10 (6.7)	9 (12.5)	0.20
Smoking	6 (2.7)	1 (0.9)	5 (6.9)	< 0.001
25(OH) D < 50 nmol/l	166 (75.1)	117 (78)	49 (69)	0.18
Medications (%)				
β-Blockers	54 (24.3)	24 (16.0)	30 (41.7)	< 0.001
ACE inhibitors	33 (14.9)	17 (11.3)	16 (22.2)	0.04
ARB	29 (13.1)	22 (14.7)	7 (9.7)	0.40
CCB	69 (31.1)	40 (26.7)	29 (40.3)	0.04
Statins	77 (34.7)	45 (30)	32 (44.4)	0.03
Insulin	46 (20.7)	22 (14.7)	24 (33.3)	0.002
Oral hypoglycemic	78 (35.1)	55 (36.7)	23 (31.9)	0.55
Anti-coagulants	11 (5.0)	6 (4.0)	5 (7.0)	0.50
Anti-platelets	63 (28.4)	38 (25.3)	25 (34.7)	0.16

Significant at $p < 0.05$

Results

Table 1 shows the differences in the characteristics of hospitalized patients according to SARS-CoV-2 status. Overall, more than 60% of the patients were males. Males were also more common among those who tested positive (65%) and slightly higher in the negative group (52.8%) (not shown in table). No significant differences were observed in age and BMI. A significantly higher prevalence of Saudis tested negative as opposed to other nationalities ($p = 0.004$). In terms of pre-existing conditions, the negative group had a significantly higher prevalence of hypertension ($p < 0.001$), DM ($p = 0.02$), CVD ($p = 0.003$), CHF ($p < 0.001$), CKD ($p < 0.001$) and smoking ($p < 0.001$) than the positive group. In terms of medications, the negative group was also more likely to use β-blocker ($p < 0.001$), ACE inhibitors

($p = 0.04$), CCB, $p = 0.04$), statins ($p = 0.03$) and insulin ($p = 0.002$). While vitamin D deficiency was highly prevalent in all patients (75.1%), no significant differences were seen between groups. The rest of the comparisons were not significant (Table 1).

Table 2 shows the unadjusted and adjusted differences in radiologic and laboratory investigations of admitted patients based on SARS-CoV-2 status. Majority of those who tested positive presented with bilateral lung infiltrates (69.3%) which was significantly higher than those who tested negative (38.5%) ($p < 0.001$). The positive group also had significantly worse liver and lipid profiles than the negative group in terms of higher AST, LDH and triglycerides (adjusted p values 0.01, < 0.001 and 0.007, respectively). On the other hand, the negative group had significantly higher levels of BUN and creatinine than the positive group (adjusted p values 0.001 and < 0.001, respectively). With regard to inflammatory profile, only CRP levels were significantly higher in the positive than the negative group (adjusted $p = 0.03$). The positive group also had significantly higher HbA1c and FBG than the negative group (adjusted p values both at 0.02). (Table 2). Lastly, the positive group had significantly lower circulating 25(OH)D levels compared to the negative group, both in unadjusted ($p = 0.025$) and adjusted ($p = 0.037$) p values. In terms of outcome, however, no significant differences were seen in the vitamin D status of those discharged versus those who died (Fig. 2).

In terms of clinical outcomes, no significant differences in groups were observed, with the exception of discharged patients, being significantly higher in the positive than the negative group (81.4 versus 65.3%; $p = 0.01$) (Table 3).

In the last Table 4, predictors for SARS-CoV-2 (+) and death were determined using multivariate logistic regression analysis. Age above 60 years, presence of bilateral lung infiltrates and most pre-existing conditions (DM, HPN, CVD, CHF and CKD) were significantly associated with higher risk for SARS-CoV-2 even after adjusting for covariates (p values < 0.05). Both vitamin D deficiency at the mild [Odds ratio, OR 1.6 (95% confidence interval, CI 0.8–3.0)] and severe levels [OR 5.3 (95% CI 0.6–45.7)] also showed increased risk but were not statistically significant in both unadjusted ($p = 0.10$) and adjusted ($p = 0.18$) models. For death, significant predictors included male sex [OR 1.4 (0.63–3.1); $p = 0.02$], CVD [OR 2.5 (1.0–6.3); p = 0.048], CKD [OR 3.2 (1.3–7.6); $p = 0.009$] and severe vitamin D deficiency [OR 4.7 (1.0–21.3); p = 0.04]. CKD was the only significant predictor for death independent of age, sex and BMI [OR 3.5 (1.4–8.7); adjusted $p = 0.008$]. Worthy to note is that severe vitamin D deficiency was also associated with mortality but at borderline significance [OR 4.9 (0.9–25.8); $p = 0.06$]. The rest of the odds ratios and are shown in Table 4.

Table 2 Clinical characteristics of Covid-19 patients on admission

Parameters	SARS-CoV-2 status		p value	
	Positive	Negative	Unadjusted	Adjusted
N	150	72		
Chest X-ray				
No infiltrates	29 (19.3)	22 (42.3)	<0.001	<0.001
Unilateral infiltrates	17 (11.3)	10 (19.2)		
Bilateral infiltrates	104 (69.3)	20 (38.5)		
Liver profile				
ALT (U/l) (20–65)[#]	52.9 ± 3.9	43.4 ± 7.7	<0.001	0.63
AST (U/l) (15–37)[#]	52.3 ± 3.2	33.2 ± 3.9	<0.001	0.01
LDH (U/l) (84–246)[#]	452.1 ± 15.0	300.5 ± 18.4	<0.001	<0.001
Renal profile				
BUN (mmol/l) (2.5–6.4)[#]	8.9 ± 0.7	13.9 ± 1.3	<0.001	0.001
Creatinine (μmol/l) (49–90)[#]	160.1 ± 17.8	331.1 ± 50.3	0.001	<0.001
Lipid profile				
Triglycerides (mmol/l)	2.0 ± 0.1	1.4 ± 0.1	0.004	0.007
HDL-cholesterol (mmol/l)	0.9 ± 0.08	1.1 ± 0.08	0.16	0.18
LDL-cholesterol (mmol/l)	2.0 ± 0.1	1.9 ± 0.2	0.55	0.80
Inflammatory profile				
Ferritin (μg/ml) (13–150)[#]	1000.9 ± 106.9	601.9 ± 149.4	<0.001	0.11
ESR (mm/h) (0–24)[#]	76.8 ± 2.7	73.4 ± 4.8	0.64	0.23
CRP (mg/l) (<10.0)[#]	110.4 ± 6.3	79.2 ± 11.9	<0.001	0.03
Glycemic profile				
HbA1c (%)	7.8 ± 0.2	7.1 ± 0.2	0.01	0.02
FBG (mmol/l)	9.7 ± 0.4	7.8 ± 0.5	0.004	0.02
RBG (mmol/l)	9.9 ± 0.4	11.3 ± 0.9	0.18	0.17
25(OH)D				
25(OH)D (nmol/l) (75–250)	35.8 ± 1.5	42.5 ± 3.0	0.025	0.037

[#]Non-normal variables; covariates include age, sex and BMI; significant at $p < 0.05$

Fig. 2 Differences in 25(OH)D levels according to **a** SARS-CoV-2 Status and **b** Outcome of hospitalized patients. Covariates for adjusted p value include age, sex and BMI
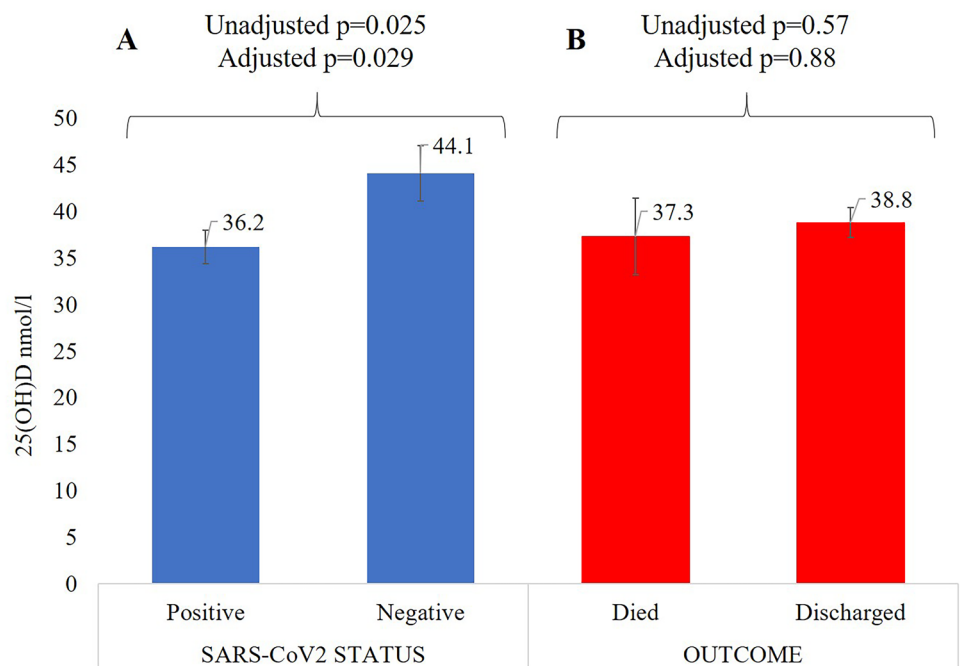
Table 3 Differences in outcomes

Outcome (%)	All	SARS-CoV-2 status		p value
		Positive	Negative	
N	222	150	72	
Intubated	30 (13.6)	24 (16.0)	6 (8.3)	0.14
Admitted in ICU	60 (27.3)	46 (30.7)	14 (19.4)	0.08
Discharged	165 (76.0)	118 (81.4)	47 (65.3)	0.01
Death	28 (12.8)	21 (14.0)	7 (9.7)	0.39

Data presented as N (%); significant at $p < 0.05$

Discussion

While the quest for effective therapies and vaccines against COVID-19 is still on-going with modest success, remedies aimed at SARS-CoV-2 prevention remain particularly imperative as the world learns to coexist with the pandemic. In the present retrospective, case–control study, results from the clinical data of hospitalized patients in Riyadh, Saudi Arabia indicate a very high prevalence of vitamin D deficiency over-all, and significantly lower 25(OH)D levels among SARS-CoV-2-positive as compared to SARS-CoV-2-negative patients. This statistical significance persisted even after adjusting for age, sex and BMI. Furthermore, severe vitamin D deficiency appears to be an independent predictor for COVID-19 mortality by as much as 5 times compared to those whose 25(OH)D levels were higher. The present study is one of the few to use confirmed SARS-CoV-2-negative patients as controls, and the first in the Arabian Gulf region.

The significantly lower 25(OH)D levels among hospitalized COVID-19 patients are in harmony with other case–control findings obtained in Spain [13] and China [16], although the controls used in the mentioned studies were apparently healthy individuals from population-based cohorts that were matched for age and sex. It also supports the growing evidence linking vitamin D deficiency with severity of COVID-19 outcomes [25–27]. A big difference in the present study as compared to other case–control investigations is that all patients were not only confirmed hospital admissions, but all have been screened for SARS-CoV-2 before stratification to positive and negative groups in the same time frame, potentially narrowing selection bias which is a limitation of previous studies.

In the present study, all the pre-existing conditions where vitamin D deficiency is known to be prevalent (DM, HPN, CVD, CHF, CKD and stroke) were significant predictors for COVID-19 infection independent of age, sex and BMI. Furthermore, CKD was an important predictor of COVID-19 mortality in the present cohort even after adjusting for established covariates. While severe vitamin D deficiency was a significant predictor of death only in the unadjusted model, the risk is nevertheless elevated even in the adjusted models, albeit at borderline significance. CKD, and kidney diseases in general, impairs vitamin D catabolism [28]. Levels of circulating 25(OH)D were observed to substantially fall parallel to decreasing glomerular filtration rate (GFR) [29]. Severe vitamin D deficiency can therefore be linked to COVID-19 mortality indirectly, depending on the extent of renal damage and existing renal disorders. The absence of significant risk in

Table 4 Significant predictors of SARS-CoV-2 (+) and death using multivariate logistic regression analysis

Predictor	SARS-CoV-2 (+)				Death			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age > 60 years	1.9 (1.1)	0.03			1.4 (0.63–3.1)	0.41		
Male	1.6 (0.9–2.9)	0.09			3.3 (1.2–9.2)	0.02		
BMI > 30 kg/m^2	1.0 (0.6–1.8)	0.99			0.7 (0.3–1.6)	0.39		
Smoking	12.5 (0.8–186)	0.07	12.8 (0.8–210)	0.08	1.2 (0.1–13.2)	0.85	1.7 (0.2–20.0)	0.66
Bilateral infiltrates	3.9 (1.9–8.2)	<0.001	3.6 (1.7–7.1)	0.001	3.2 (0.9–11.2)	0.07	2.9 (0.8–10.9)	0.11
DM	2.1 (1.2–3.8)	0.01	2.1 (1.1–4.0)	0.02	1.6 (0.7–3.6)	0.25	1.7 (0.7–4.0)	0.26
HPN	3.4 (1.8–6.2)	<0.001	3.2 (1.6–6.4)	0.001	1.2 (0.5–2.6)	0.69	1.0 (0.4–2.6)	0.99
CVD	3.2 (1.5–6.8)	0.002	3.2 (1.4–7.2)	0.004	2.5 (1.0–6.3)	0.048	2.3 (0.8–6.1)	0.10
CHF	12.8 (4.6–36)	<0.001	13.8 (4.7–39.9)	<0.001	1.7 (0.6–4.8)	0.35	1.4 (0.4–4.3)	0.58
CKD	4.5 (2.2–9.2)	<0.001	3.8 (1.8–8.2)	0.001	3.2 (1.3–7.6)	0.009	3.5 (1.4–8.7)	0.008
Stroke	2.0 (0.8–5.2)	0.15	1.7 (0.6–4.9)	0.29	2.3 (0.7–7.5)	0.18	2.0 (0.5–7.1)	0.35
25(OH)D < 50 nmol/l	1.6 (0.8–3.0)	0.15	1.4 (0.7–2.8)	0.30	1.2 (0.5–2.9)	0.67	1.3 (0.5–3.2)	0.61
25(OH)D < 12.5 nmol/l	5.3 (0.6–45.7)	0.10	4.5 (0.5–39.4)	0.18	4.7 (1.0–21.3)	0.04	4.9 (0.9–25.8)	0.06

Covariates entered in the model: sex, age and BMI; significant at $p < 0.05$

mortality observed in SARS-CoV-2-positive patients with DM alone and/or obesity alone has been documented in similar retrospective studies done within the Arab Gulf region [19, 30], and suggests that the increased risk for COVID-19 death is multifactorial and is probably associated more on the cumulative effects of DM and/or obesity clustering with other chronic diseases, or cardiometabolic multi-morbidity, which are exacerbated in acute complications [31].

Finally, it is worthy to note that more men had COVID-19 than women in the present study, confirming other retrospective studies done in Saudi Arabia where males also had worse outcomes than their female counterparts [19, 30]. The male sex being an independent risk factor for SARS-CoV-2 can be attributed to many factors, but mostly for the lack of immune-boosting estrogen. 17β-estradiol, in particular, a female hormone in which biosynthesis is regulated by vitamin D via calcium homeostasis [32], has many physiologic actions in terms of the RAS system activation, anti-inflammation, anti-viral protection and endolysosomal degradation [33].

The authors acknowledge some limitations. The lack of statistical significance in eliciting an association between severe vitamin D deficiency and mortality was clearly due to low sample size. Furthermore, the findings only apply to hospitalized patients with pre-existing conditions and not the general community to eliminate selection bias (Berkson's). This is especially true in the present study, given the nature of 25(OH)D as a negative acute-phase reactant for both acute and chronic inflammatory-state diseases [34, 35]. Having mentioned such, it is nevertheless safe to assume that the majority of the participants already had vitamin D deficiency, given their age and pre-existing conditions, all of which are associated with chronic, low-grade systematic inflammation [36]. Lastly, the nature of the retrospective design and the small number of admitted patients swabbed made it difficult to properly match the positive and negative cases, hence the discrepancy in the presence of pre-existing conditions. Nevertheless, the study is the first of its kind to compare the clinical characteristics of hospitalized patients screened for SARS-COV2 in the Gulf region, and to demonstrate differences and associations of vitamin D levels to COVID-19 and mortality among hospitalized patients.

In summary, the prevalence of vitamin D deficiency among hospitalized patients screened for SARS-CoV-2 in Saudi Arabia is remarkably high and is significantly lower in SARS-CoV-2-positive patients, even after adjusting for covariates known to influence vitamin D. Severe vitamin D deficiency, however, is not associated with SARS-CoV-2 infection and is more related to increased mortality risk. The present findings support large-scale clinical trials to confirm whether manipulating vitamin D status through supplementation offers beneficial effects in COVID-19 prevention and treatment, particularly among high-risk individuals living in regions where both vitamin D deficiency and SARS-CoV-2 infection are highly prevalent.

Declarations

Conflict of interest The authors declare no conflict of interest.

Statement of human and animal rights All procedures reported comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Ethical approval Ethical approval and waiver of informed consent were obtained from the Institutional Review Board (IRB) of the College of Medicine in King Saud University (KSU) in Riyadh, Saudi Arabia (E-20-5090/July 5, 2020).

Informed consent Not applicable.

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