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Original Article

Vaccination and vitamin D in relation to disease severity and mortality in patients with COVID-19 disease: a follow-up study

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Abstract

The emergence of Coronavirus Disease 2016 (COVID-16), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly escalated into a global pandemic, resulting in millions of confirmed cases and deaths worldwide. The objective of this study was to examine the effects of vitamin D and vaccination on mortality and disease severity in patients with COVID-16. In this cross-sectional study, we observed the suspected and confirmed admitted patients with COVID-19 for the possible outcomes after admission to the hospital. The study included patients with a mean age of 71.01 years (range: 28–66), predominantly aged ≥60 years (85.14%) and male (85.05%). Most patients were unvaccinated (77.03%) upon admission. Admission duration ranged from 1–30 days, with the highest proportion staying 8–14 days (36.16%), followed by 1–3 days and >14 days (each 21.62%). Symptoms appeared 1–46 days pre-admission (median: 8 days). Disease severity was critical (41.86%), severe (28.38%), moderate (25.68%), and mild (4.05%). All patients required oxygen. Mortality was 54.05%, 32.43% were discharged unknown, and 13.51% recovered. Key comorbidities included hypertension (66.22%), diabetes (37.84%), IHD (25.68%), smoking (21.62%), and CKD (12.16%). Universal fever presentation included persistent (44.63%) and moderate (28.66%) types. Common symptoms were shortness of breath (66.67%), cough (75.68%), chest pain (60.81%), fatigue (52.7%), and anorexia (50.0%). Vaccination (22.67%) and vitamin D status showed no significant association with disease severity or outcomes. Most patients were elderly, male, unvaccinated, and had comorbidities; high mortality was observed, with no significant association between outcomes and vaccination or vitamin D status.

Keywords: COVID-16, Severity, Mortality, Outcome, Vaccination, Serum vitamin D levels.

1. Introduction

The emergence of Coronavirus Disease 2016 (COVID-16), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly escalated into a global pandemic, resulting in millions of confirmed cases and deaths worldwide [1, 2]. Despite significant advancements in therapeutic strategies and widespread vaccine deployment, COVID-16 continues to pose a major global healthcare challenge, driving ongoing research efforts to identify new solutions for combating the disease and improving patient outcomes [1-3].

Among the various potential interventions, vitamin D supplementation has garnered substantial interest due to its well-documented role as a steroid hormone involved in modulating the immune response and reducing inflammation [2, 4]. Physiological actions of vitamin D, particularly in its active form calcitriol, include stimulating immune cells to produce antimicrobial peptides like cathelicidin and defensins, which interfere with viral entry into host cells [2, 5]. Additionally, vitamin D is associated with shifting the immune system from a pro-inflammatory state to an anti-inflammatory one by upregulating anti-inflammatory cytokines and decreasing pro-inflammatory ones, such as IL-1, IL-6, and TNF-α, which are implicated in the harmful cytokine storm seen in severe COVID-19 [6, 7]. Furthermore, vitamin D interacts with the renin-angiotensin-aldosterone system (RAAS), potentially reducing vasoconstriction and acute respiratory distress syndrome (ARDS) [8]. Early in the pandemic, numerous observational studies and meta-analyses suggested an inverse relationship between vitamin D deficiency (hypovitaminosis D) and an increased risk of acquiring SARS-CoV-2 infection, higher disease severity, and increased mortality rates in COVID-16 patients [3]. These findings were particularly pronounced in vulnerable populations, including the elderly and those with comorbidities like diabetes and hypertension [2].

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However, the efficacy of vitamin D supplementation in improving clinical outcomes for COVID-16 patients remains inconsistent across various studies. While some systematic reviews and meta-analyses of randomized controlled trials (RCTs) have reported that vitamin D significantly reduced ICU admissions and lowered the need for mechanical ventilation [9], others found no significant effect on hospital stay length, ICU stay length, mechanical ventilation duration, mortality, or the need for supplemental oxygen [10]. These discrepancies are often attributed to heterogeneous study designs, varied patient characteristics (e.g., baseline vitamin D status, age, comorbidities), and differences in vitamin D dosage and formulation [1].

Alongside vitamin D, COVID-16 vaccination has been crucial in reducing the severity and spread of the disease [3]. Vaccines are designed to trigger immune responses, which may alleviate disease progression, organ failure, and death [11]. However, in some contexts, studies have found no significant association between vaccination status and patient outcomes or disease severity in hospitalized COVID-16 patients [12]. This could be due to factors such as low vaccination rates among the hospitalized cohort, the severity of the clinical presentation in those admitted, or the specific characteristics of the study population [12]. Furthermore, the interplay between vitamin D status and vaccine efficacy has been investigated, with some studies suggesting that adequate vitamin D levels may influence the immune response to SARS-CoV-2 vaccines, particularly for long-term antibody persistence [13], while other large trials found no significant influence of vitamin D supplementation on vaccine efficacy or immunogenicity [14].

Given these mixed and sometimes contradictory findings regarding the impact of vitamin D and the varied observations on vaccine effectiveness in specific patient populations, a comprehensive investigation into their combined and individual effects on COVID-16 outcomes is warranted. Understanding these relationships is particularly crucial in cohorts where patients present with complex health profiles, such as advanced age and multiple comorbidities, which are known risk factors for both severe COVID-16 and vitamin D deficiency. Such research can help clarify existing ambiguities and inform more targeted clinical guidelines and public health strategies. The objective of this study was to examine the effects of vitamin D and vaccination on mortality and disease severity in patients with COVID-16.

2. Materials and methods

2.1 Study design and setting

This cross-sectional observational study was conducted over six months, from February to July 2022, involving hospitalized patients with suspected or confirmed COVID-19. Participants were recruited from medical facilities, where blood samples were collected and target variables were measured. Patients were monitored for potential outcomes during their hospital stay.

This study was conducted in Duhok Governorate, Kurdistan Region of Iraq. Sample collection was carried out at two public hospitals—Corona Infectious Diseases Hospital and Lalav COVID-19 Hospital—and two private facilities: Shilan Private Hospital and Vin Medical Complex, all of which admit hospitalized COVID-19 patients.

2.2 Sampling and population

A total of 74 adult individuals (>18 years) of both sexes, residing in Duhok City and presenting with symptoms of upper or lower respiratory tract infections, were enrolled in the study. All participants were suspected of SARS-CoV-2 infection and provided data through a standardized questionnaire.

2.3 Inclusion and exclusion criteria

Inclusion criteria consisted of hospitalized patients aged 18 years and older of both genders, diagnosed or suspected of having SARS-CoV-2 via PCR testing. Exclusion criteria included individuals without signs or symptoms of COVID-19, those who received their last vaccine dose less than six months prior, and pregnant women.

2.4 Ethical considerations

This study was approved by the Ethical Committee of the Duhok General Directorate of Health, registered as reference number 16222022-1-4 on 16 February 2022. Written informed consent was obtained from all participants following a clear explanation of the study's aims and procedures. Participant confidentiality was maintained by assigning unique identification codes, removing personal identifiers from the dataset, and securely storing all data.

2.5 Data collection methods

The study collected clinical information, demographic characteristics, and laboratory results using structured questionnaires and hospital patient records. Data were obtained systematically to ensure comprehensive assessment of patients' conditions and disease outcomes.

2.6 Questionnaire

All participants completed an interviewer-administered, structured questionnaire focused on key areas: demographics, risk factors, clinical manifestations, disease severity, duration and timing of symptoms, length of hospital stay, need for ventilation, and vaccination history. This standardized tool ensured consistent and comprehensive data collection for the study.

The questionnaire incorporated validated tools and adhered to the National Institutes of Health (NIH) guidelines for assessing COVID-19 severity. Based on NHS criteria, patients were categorized into five levels: asymptomatic (no symptoms), mild (presence of symptoms such as fever, cough, fatigue, sore throat, myalgia, headache, gastrointestinal issues, or loss of taste/smell without shortness of breath), moderate (evidence of lower respiratory disease clinically or radiographically with SpO_2 ≥94% on room air at sea level), severe (SpO_2 <94%, respiratory rate >30 breaths/min, or lung infiltrates >50%), and critical (respiratory failure, septic shock, or multiple organ dysfunction) [15].

2.7 Serological analysis of serum vitamin D level

A blood sample is typically drawn from a vein in the arm to measure the level of 25-hydroxyvitamin D [25(OH)D], the main circulating form of vitamin D in the body. After collection, the sample is analyzed in the laboratory using methods such as immunoassay or mass spectrometry to accurately determine 25(OH)D concentration. This measurement serves as a reliable indicator of an individual's vitamin D status, enabling the assessment of deficiency or

sufficiency.

3. Statistical analyses

The general and medical characteristics of suspected and confirmed COVID-19 patients were presented as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. The prevalence of risk factors, symptoms, disease severity, vitamin D deficiency, and clinical outcomes was reported as numbers and percentages. Associations between patient outcomes, disease severity, and both vaccination status and vitamin D levels were assessed using Pearson's chi-squared test. A p-value <

0.05 was considered statistically significant. All statistical analyses were performed using JMP® software, Version 18.0 (SAS Institute Inc., Cary, NC, 1989–2023).

4. Results

The mean age of the patients was 71.01, ranging between 28 and 66 years old. The age groups of the patients were <60 years. (14.86%) and ≥ 60 yrs. (85.14%). The patients were males (85.05%) and females (45.65%). The patients lived in Duhok City (31.08%) and other areas inside Duhok Governorate (68.62%). The patients were recruited from Corona Hospital (86.16%), Lalav Hospital (6.76%), and private hospitals (4.05%). Most of the suspected patients with COVID-16 disease were confirmed to have COVID-16 disease by a PCR test (76.73%). Some patients were confirmed to have a negative PCR test (13.51%) and 5 patients were postponed due to unknown reasons. All patients were admitted to the hospital in the ICU (36.16%) or a medical ward (60.81%). The admission duration was mostly between 8 and 14 days (36.16%), followed by 1-3 days (21.62%) and >14 days (21.62%) and 4-7 days (17.57%). Our study showed that 54.05% of the patients died of the COVID-16 disease in the hospital and 32.43% were discharged with unknown outcome (elective by the family members of the patients or by the clinicians) and 13.51% recovered from the disease. The admission duration was between 1 and 30 days. The patients had symptoms before admission between 1 and 46 days for a median of 8 days. The study showed that most of the patients had critical level (41.86%), followed by severe (28.38%), moderate (25.68%), and mild levels (4.05%). All patients received an O2 supply. The types of received ventilations were Reservoir Face Mask (56.76%), followed by CPAP (36.46%), and nasal mask (6.76%; Table 1).

The most prevalent risk factors in patients with or suspected COVID-16 disease were hypertension (66.22%), diabetes mellitus (37.84%), IHD (25.68%), and smoking

Table 1. General and medical characteristics of the patients with or suspected of COVID-19 disease.

Characteristics (n=74)		Frequency destruction	
		Number	Percentage
Age (28-GG years)	Std Err Mean: 1.57	71.01	13.53
Age groups	<60 yrs.	11	14.86
	≥ 60 yrs.	63	85.14
Gender	Male	40	54.05
	Female	34	45.65
Residency	Duhok	23	31.08
	Other areas	51	68.62
Health Facility	Corona Hospital Lalav	66	86.16
	Private hospitals	5	6.76
		3	4.05
PCR COVID	Negative Positive	10	13.51
		56	76.73
	Postponed	5	6.76
Admission Hospitalization	Yes	74	100
admission	1-3 days	16	21.62
	4-7 days	13	17.57
	8-14 days	26	36.16
	>14 days	16	21.62
Admission Duration	1-30 days	6.30	5.67
Setting	ICU	26	36.16
	Ward	45	60.81
Patient Outcome	Died	40	54.05
	Discharged	24	32.43
	Recovered	10	13.51
Symptom Duration (pre-admission)	1-46	Median: 8	MAD: 3
Disease Severity	Mild	3	4.05
	Moderate	16	25.68
	Severe	21	28.38
	Critical	31	41.86
O2 Supply	Yes	74	100
Type of Ventilation	CPAP	27	36.46
	Nasal Mask	5	6.76
	Reservoir Face Mask	42	56.76

(21.62%). The CKD was found in 12.16% of the patients (Table 2; Fig. 1).

The study showed that all patients had fever with different severities, including mostly persistent (44.63%) and moderate (28.66%). The most prevalent symptoms of the COVID-16 disease were shortness of breath (66.67%), cough (75.68%), chest pain (60.81%), fatigue (52.7%), Anorexia (50.0%), Constipation (44.56%), Myalgia (44.56%), insomnia (44.56%), and Interscapular Pain (33.78%; Table 3; Fig 2).

The study found that most of the patients were unvaccinated on admission (77.03%) and only 22.67% had received the vaccination before admission. The types of the received vaccinations were AstraZeneca (35.26%), Pfizer (41.18%), and Sinopharm (23.53%). Most of the patients received two doses of the vaccine (82.35%), followed by one dose (11.76%) and three doses (5.88%). The vitamin D status in admitted COVID-16 patients was deficient (68.62%), insufficient (17.57%), and sufficient (13.51%; Table 4).

The study showed that the outcomes of the patients in COVID-16 were not associated with vitamin D status (p=0.0633) and vaccination (p=0.2048; Table 5).

In addition, the study showed that the disease severity was not associated with vitamin D status (p=0.7615) and vaccinations (p=0.0713; Table 6).

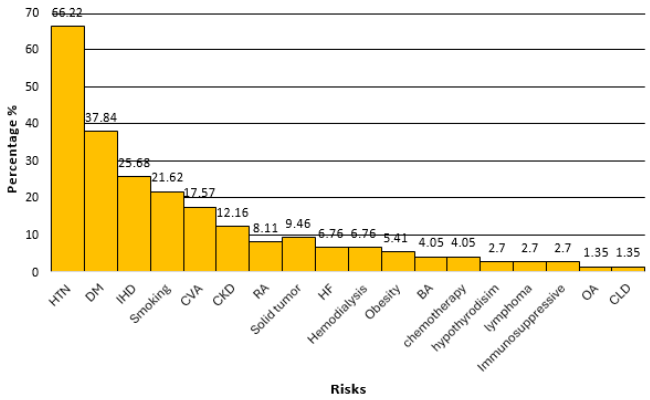

Fig. 1. Risks in patients with or suspected of COVID-19 disease.

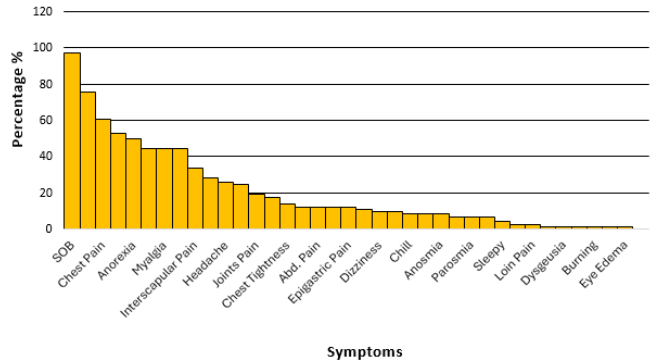

Fig. 2. Symptoms of patients with or suspected COVID-19 disease.

5. Discussion

The global COVID-16 pandemic, caused by the SARS-CoV-2 virus, has profoundly impacted global health since its emergence in December 2016 [1]. Despite significant advancements in therapeutic strategies and widespread vaccine deployment, the search for effective interventions and a deeper understanding of contributing factors to disease severity and outcomes remains crucial [1]. This study investigated the clinical course and outcomes of a cohort of COVID-16 patients, focusing on the influence of patient demographics, comorbidities, vitamin D status, and vaccination status. Our findings present a unique picture, particularly regarding the lack of association between vitamin D status, vaccination, and patient outcomes, which warrants extensive discussion in light of existing literature.

The patient cohort in this study was characterized by a high mean age of 71.01 years, with a substantial majority (85.14%) being 60 years or older. This demographic profile

Table 2. Risk factors in patients with or suspected of COVID-19 disease.

	Frequency distribution no. (%)	
Risks (n=74)	**No**	**Yes**
HTN	25 (33.78)	46 (66.22)
DM	46 (62.16)	28 (37.84)
IHD	55 (74.32)	16 (25.68)
Smoking	58 (78.38)	16 (21.62)
CVA	61 (82.43)	13 (17.57)
CKD	65 (87.84)	6 (12.16)
RA	68 (61.86)	6 (8.11)
Solid tumor	67 (60.54)	7 (6.46)
HF	66 (63.24)	5 (6.76)
Hemodialysis	66 (63.24)	5 (6.76)
Obesity	70 (64.56)	4 (5.41)
BA	71 (65.65)	3 (4.05)
chemotherapy	71 (65.65)	3 (4.05)
hypothyrodisim	72 (67.30)	2 (2.70)
lymphoma	72 (67.30)	2 (2.70)
Immunosuppressive	72 (67.30)	2 (2.70)
OA	73 (68.65)	1 (1.35)
CLD	73 (68.65)	1 (1.35)

Table 3. Symptoms of patients with or suspected of COVID-19 disease.

Symptoms (n=74)	Frequency distribution no. (%)	
	Number	Percent
Fever		
Low-grade	1	1.45
Moderate	20	28.66
High	17	24.64
Persistent	31	44.63
SOB		
No	2	3.03
At rest	17	25.76
On Exertion	17	25.76
Severe	30	45.45
Cough	56	75.68
Chest Pain	45	60.81
Fatigue	36	52.7
Anorexia	37	50
Constipation	33	44.56
Myalgia	33	44.56
Insomnia	33	44.56
Interscapular Pain	25	33.78
Backache	21	28.38
Headache	16	25.68
Nausea	18	24.32
Joints Pain	14	18.62
Dry Mouth	13	17.57
Chest Tightness	10	13.51
Vomiting	6	12.16
Abd. Pain	6	12.16
General body pain	6	12.16
Epigastric Pain	6	12.16
Voice Change	8	10.81
Dizziness	7	6.46
Flu Like Illness	7	6.46
Chill	6	8.11
Diarrhea	6	8.11
Anosmia	6	8.11
Sore Throat	5	6.76
Parosmia	5	6.76
Ageusia	5	6.76
Sleepy	3	4.05
Rigor	2	2.7
Loin Pain	2	2.7
Sweating	1	1.35
Dysgeusia	1	1.35
Vertigo	1	1.35
Burning	1	1.35
Eye Pain	1	1.35
Eye Edema	1	1.35
Nasal Obstruction	0	0

Table 4. Vaccination, vitamin D and outcome status in patients with or suspected COVID-19 disease.

Vaccination and outcome (n=74)	Frequency distribution no. (%)	
	Number	**Percentage**
Vaccination		
Unvaccinated	57	77.03
Vaccinated	17	22.67
Vaccine type		
AstraZeneca	6	35.26
Pfizer	7	41.18
Sinopharm	4	23.53
Vaccination Dose		
one dose	2	11.76
two doses	14	82.35
three	1	5.88
Vitamin D status		
Deficient	51	68.62
Insufficient	13	17.57
sufficient	10	13.51

Table 5. Associations of patient outcomes with vitamin D and vaccination status in patients with or suspected of COVID-19 disease.

vitamin D and vaccination status (n=74)	Patient Outcome			
	Died (n=40)	**Discharged (n=24)**	**Recovered (n=10)**	**p**
Vitamin D status				
deficient	31 (60.78)	12 (23.53)	8 (15.66)	0.0633
insufficient	7 (53.85)	5 (38.46)	1 (7.66)	
sufficient	2 (20.00)	7 (70.00)	1 (10.00)	
Vaccination				
Unvaccinated	34 (56.65)	16 (28.07)	7 (12.28)	0.2048
Vaccinated	6 (35.26)	8 (47.06)	3 (17.65)	
Vaccine type				
AstraZeneca	2 (33.33)	3 (50.00)	1 (16.67)	0.6258
Pfizer	3 (42.86)	2 (28.57)	2 (28.57)	
Sinopharm	1 (25.00)	3 (75.00)	0 (0.00)	
Vaccination Dose				
one dose	1 (50.00)	0 (0.00)	1 (50.00)	0.4762
two doses	5 (35.71)	7 (50.00)	2 (14.26	
three	0 (0.00)	1 (100)	0 (0.00)	

Table 6. Associations of disease severity with vitamin D and vaccination status in patients with or suspected of COVID-19 disease.

vitamin D and vaccination status (n=74)	Disease Severity				
	Critical (n=31)	**Mild (n=3)**	**Moderate (n=1G)**	**Severe (n=21)**	**p**
Vitamin D status					
deficient	23 (45.10)	2 (3.62)	14 (27.45)	12 (23.53	0.7615
insufficient	5 (38.46)	1 (7.66)	2 (15.38)	5 (38.46)	
sufficient	3 (30.00)	0 (0.00)	3 (30.00)	4 (40.00)	
Vaccination					
Unvaccinated	26 (45.61)	1 (1.75)	12 (21.05)	18 (31.58)	0.0713
Vaccinated	5 (26.41)	2 (11.76)	7 (41.18)	3 (17.65)	
Vaccine type					
AstraZeneca	2 (33.33)	0 (0.00)	3 (50.00)	1 (16.67)	0.8037
Pfizer	2 (28.57)	1 (14.26)	2 (28.57)	2 (28.57)	
Sinopharm	1 (25.00)	1 (25.00)	2 (50.00)	0 (0.00)	
Vaccination Dose					
one dose	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	0.8526
two doses	4 (28.57)	2 (14.26)	5 (35.71)	3 (21.43)	
three	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	

aligns with numerous studies identifying older age as a significant independent risk factor for increased susceptibility to severe COVID-16, hospitalization, and mortality [2, 16, 17]. The cohort also exhibited a high prevalence of comorbidities, with hypertension (66.22%), diabetes mellitus (37.84%), ischemic heart disease (IHD) (25.68%), and smoking (21.62%) being the most common. These chronic conditions, including chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD), are well-established predictors for higher disease severity, intensive care unit (ICU) admission, and increased mortality in COVID-16 patients. For instance, one systematic review highlighted hypertension as a significant factor for severe disease and mortality, while COPD was identified as a strong predictor for severity, ICU admission, and mortality [18]. The high burden of pre-existing health conditions in our cohort, therefore, predisposes patients to a more complicated disease trajectory, consistent with findings that chronic systemic inflammation can exacerbate COVID-16 outcomes [19, 20].

The clinical presentation of our patients indicated a high disease severity, with 41.86% classified as critical and 28.38% as severe. All patients required oxygen supply, and symptoms such as shortness of breath (66.67%), cough (75.68%), and chest pain (60.81%) were highly prevalent. These manifestations are consistent with the respiratory nature of SARS-CoV-2 infection and often necessitate hospitalization and critical care, reflecting the substantial effects of COVID-16 on respiratory health [1, 7, 17]. The high severity in our cohort likely contributes to the remarkably high mortality rate of 54.05%, with only 13.51% recovering. This mortality rate is considerably higher than some global statistics [1, 12], but can be understood in the context of our patient population's advanced age, numerous comorbidities, and critical disease status upon admission, all of which are documented risk factors for negative outcomes [16].

A central finding of our study was the absence of a significant association between vitamin D status and patient outcomes or disease severity. This result stands in contrast to a considerable body of literature that suggests an inverse relationship between low vitamin D levels and adverse COVID-16 outcomes. Many studies have indicated that hypovitaminosis D is associated with an increased risk of acquiring SARS-CoV-2 infection and poor prognosis, including higher rates of severe disease, hospitalization, ICU admission, and mortality [17]. For instance, a meta-analysis of 14 randomized controlled trials (RCTs) found that vitamin D significantly reduced ICU admissions and lowered the need for mechanical ventilation [1]. Similarly, an observational study in the UAE found that serum 25(OH) D levels below 12 ng/mL were significantly associated with a higher risk of severe COVID-16 and death [21].

Conversely, some reviews and meta-analyses, particularly those focusing solely on RCTs, have reported inconsistent or non-significant effects of vitamin D supplementation on clinical outcomes such as hospital and ICU stay length, mechanical ventilation duration, or mortality [1, 2, 14, 22]. Our result aligns with this latter group, suggesting that in our specific cohort, vitamin D status did not emerge as a distinguishing factor for disease severity or outcomes. This discrepancy could be attributed to several factors, including the high baseline severity of illness in our cohort, where the disease progression might have been too advanced for vitamin D to exert a noticeable mitigating effect. Differences in study design (e.g., observational vs. RCTs), patient characteristics, timing and dosage of vitamin D intervention, and definitions of vitamin D deficiency can also lead to varied conclusions across studies [1, 22, 23].

Furthermore, our study found no association between vaccination status and patient outcomes or disease severity. This finding is particularly striking, as it contradicts the overwhelming evidence supporting the protective efficacy of COVID-16 vaccines against severe disease, hospitalization, and mortality [12, 16]. Numerous studies have demonstrated a substantial reduction in hospitalization and death rates among vaccinated individuals compared to unvaccinated ones [12, 24]. For instance, a study in Spain reported significantly higher mortality rates in unvaccinated confirmed cases [25]. However, our result echoes a study conducted in Iraqi Kurdistan that also found no significant association between receiving vaccination and patient outcomes or disease severity, a finding attributed to a small sample size for vaccinated patients. In our cohort, a large majority of patients (77.03%) were unvaccinated, with only 22.67% having received vaccination prior to admission. The high age and comorbidity burden in our cohort, coupled with the critically ill nature of the admitted patients, might have masked the protective benefits of vaccination. It is recognized that older adults and individuals with multiple chronic diseases can have compromised immune responses to vaccines, potentially leading to less effective protection [12]. Therefore, while vaccines generally offer strong protection, their impact might be attenuated in a highly vulnerable, severely ill population, or the sample size of vaccinated individuals was insufficient to detect a statistically significant difference.

Considering the interplay between vitamin D and vaccination, some literature suggests that adequate vitamin D levels might enhance the immune response to SARS-CoV-2 vaccination, potentially leading to more sustained antibody titers [14, 16, 26, 27]. One study specifically observed that low vitamin D levels in vaccinated older adults were associated with a survival rate similar to that of unvaccinated individuals and significantly lower than that of vaccinated individuals with high vitamin D levels [22]. While our study did not assess vitamin D levels stratified by vaccination status, this concept provides a plausible hypothesis: if the vaccinated individuals in our cohort also had low vitamin D levels, this could contribute to the observed lack of association between vaccination and improved outcomes.

This study possesses several limitations. Firstly, it is an observational study, which limits the ability to establish causality between the studied factors and outcomes. The relatively small sample size, particularly for vaccinated individuals, may have also restricted the statistical power to detect subtle associations, similar to the limitations highlighted in another regional study [12]. Additionally, our study did not specify the type or number of vaccine doses received by vaccinated patients, nor did it track vitamin D levels over time or the specific dosages of vitamin D supplementation (if any) prior to admission. The high prevalence of comorbidities and critical illness at admission also introduces confounding factors that are difficult to fully adjust for, and the advanced stage of the disease might have overshadowed any potential benefits from vitamin D or vaccination.

In conclusion, our study identifies advanced age, high comorbidity burden, and critical disease severity as prominent characteristics of our hospitalized COVID-16 patient cohort, leading to a high mortality rate.

However, our findings that vitamin D status and vaccination were not associated with patient outcomes or disease severity stand in partial contradiction to much of the existing global literature. These results may reflect the unique vulnerabilities of our specific patient population and the advanced stage of their illness at the time of assessment, or they may highlight the complex interplay of various factors that influence COVID-16 prognosis. Future large-scale randomized controlled trials, particularly focusing on highly vulnerable populations and carefully controlling for confounding variables, are necessary to further elucidate the definitive roles of vitamin D supplementation and vaccination in mitigating COVID-16 severity and improving outcomes in such challenging clinical contexts.

In conclusion, this study found no significant association between vitamin D status or COVID-19 vaccination and the severity or mortality outcomes in hospitalized patients with COVID-19. The high prevalence of advanced age, multiple comorbidities, and critical illness among patients likely overshadowed any potential protective effects of vitamin D or vaccination within this cohort. These findings highlight the complexity of COVID-19 clinical outcomes and suggest that further large-scale, controlled studies are needed to clarify the roles of vitamin D supplementation and vaccination in diverse patient populations. Nonetheless, maintaining adequate vitamin D levels and vaccination remain important public health measures in managing COVID-19 risk.

Conflict of interests
The authors do not declare any conflicts of interest.

Consent for publications
We obtained the consent of the patients for the publication of the data.

Ethics approval and consent to participate
This study was approved by the Ethical Committee of the Duhok General Directorate of Health, registered as reference number 16222022-1-4 on 16 February 2022. Written informed consent was obtained from all participants following a clear explanation of the study's aims and procedures. Participant confidentiality was maintained by assigning unique identification codes, removing personal identifiers from the dataset, and securely storing all data.

Informed consent
We obtained the written consent forms from all patients before inclusion in the study.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
Aleen Sardar AL-NOORI: design, concept, review, data collection, writing first draft, data analysis; **Ahmed Mohamed Salih:** concept, design, supervision, data analysis, and final approval; **Muayad Aghali Merza:** concept, design, supervision, data analysis, and final approval

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None.

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