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RESEARCH ARTICLE

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In-hospital mortality in SARS-CoV-2 stratified by serum 25-hydroxy-vitamin D levels: A retrospective study

Mohammed Al-Jarallah[1] | Rajesh Rajan[1] | Raja Dashti[1] | Ahmad Al Saber[2] | Jiazhu Pan[2] | Kobalava D. Zhanna[3] | Hassan Abdelnaby[4] | Wael Aboelhassan[5] | Farah Almutairi[6] | Mohammed Abdullah[7] | Naser Alotaibi[8] | Mohammad Al Saleh[6] | Noor Al Nasrallah[8] | Bader Al-Bader[6] | Haya Malhas[9] | Maryam Ramadhan[10] | Mahdy Hamza[11] | Peter A. Brady[12] | Ibrahim Al-Zakwani[13] | Moudhi Alroomi[7]

[1]Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City, Kuwait

[2]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

[3]Department of Internal Medicine with the Subspecialty of Cardiology and Functional Diagnostics Named after V.S. Moiseev, Institute of Medicine, Peoples' Friendship University of Russia (RUDN University), Moscow, Russian Federation

[4]Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt, Division of Gastroenterology, Department of Medicine, Al Sabah Hospital, Kuwait

[5]Division of Gastroenterology, Department of Medicine, Jaber Al Ahmed Hospital, South Surra, Kuwait

[6]Department of Medicine, Farwaniya Hospital, Farwaniya, Kuwait

[7]Department of Infectious Diseases, Infectious Diseases Hospital, Shuwaikh Medical Area, Kuwait City, Kuwait

[8]Department of Medicine, Al Adan Hospital, Hadiya, Kuwait

[9]Department of Emergency Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

[10]Department of Obstetrics and Gynaecology, Maternity Hospital, Shuwaikh, Kuwait

[11]Department of Medical Imaging, Al Adan Hospital, Hadiya, Kuwait

Abstract

This study is done to estimate in-hospital mortality in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) stratified by Vitamin-D (Vit-D) levels. Patients were stratified according to by serum 25-hydroxy-vitamin D (25(OH) Vit-D) levels into two groups, that is, 25(OH)Vit-D less than 40 nmol/L and 25(OH) Vit-D greater than 40 nmol/L. A total of 231 patients were included. Of these, 120 (50.2%) of the patients had 25(OH)Vit-D levels greater than 40 nmol/L. The mean age was 49 ± 17 years, and 67% of the patients were males. The median length of overall hospital stay was 18 [6; 53] days. The remaining 119 (49.8%) patients had a 25(OH)Vit-D less than 40 nmol/L. Vitamin D levels were seen as deficient in 63% of patients, insufficient in 25% and normal in 12%. Overall mortality was 17 patients (7.1%) but statistically not significant among the groups ($p = 0.986$). The Kaplan–Meier survival analysis showed no significance based on an alpha of 0.05, $LL = 0.36$, $df = 1$, $p = 0.548$, indicating Vitamin_D_Levels was not able to adequately predict the hazard of Mortality. In this study, serum 25(OH)Vit-D levels were found have no significance in terms of predicting the in-hospital mortality in patients with SARS-CoV-2.

KEYWORDS

COVID-19, in-hospital mortality, SARS-CoV-2, vitamin D

Abbreviations: 25(OH)Vit-D, 25-hydroxy-vitamin D; aOR, adjusted odds ratio; CRF, case record form; CI, confidence interval; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

[12]Department of Cardiology, Illinois Masonic Medical Center, Chicago, Illinois, USA

[13]Department of Pharmacology and Clinical Pharmacy, College of Medicine & Health Sciences, Gulf Health Research, Sultan Qaboos University, Muscat, Oman

Correspondence
Rajesh Rajan, Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City 15003, Kuwait.
Email: cardiology08@gmail.com

1 | INTRODUCTION

Serum vitamin D levels in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) range between 23% and 80%.[1,2] Lower levels of Vitamin D have been associated with a greater inflammatory response in SARS-CoV-2 infection.[3] Vitamin D deficiency has been reported to be a marker of poor prognosis in SARS-CoV-2 related respiratory infections.[4] while vitamin D levels were shown to have an impact on viral respiratory tract infections.[5] Vitamin D corrections have an impact reduction of viral infections as shown in a meta-analysis.[6] The incidence of SARS-CoV-related pneumonia was reportedly higher amongst individuals with lower levels of vitamin D.[7]

2 | MATERIALS AND METHODS

The study comprised a total of 239 confirmed SARS-CoV-2 infected patients, both Kuwaitis and non-Kuwaitis above the age of 18, who were enrolled in this retrospective cohort study between February 26 and September 8, 2020. All data were obtained from electronic medical records from two tertiary care hospitals in Kuwait, Jaber Al-Ahmed Hospital and Al Adan General Hospital.

SARS-CoV-2 infection was confirmed by a positive reverse transcription-polymerase chain reaction swab from the nasopharynx. Care of all patients was standardized according to protocol by the Ministry of Health in Kuwait. The standing committee for coordination of health and medical research at the Ministry of Health in Kuwait approved the protocol and waived the requirement of informed consent (Institutional review board number 2020/1422. Patients were stratified by serum 25-hydroxy-vitamin D (25(OH)Vit-D) levels into low Vit-D level (<40 nmol/L) and high Vit D level (> 40 nmol/L).

Serum vitamin D levels less than 50 nmol/L were considered vitamin-D deficient, 50–72 nmol/L as vitamin-D insufficient, and levels more than 75 nmol/L were considered normal.[8]

The primary outcome measured was coronavirus disease 2019-related death as defined by ICD 10 code U07.1. Clinical and laboratory variables collected were: sociodemographic determinants, co-morbidity, clinical presentation, laboratory results, and duration of intensive care unit (ICU) and in-hospital stay. An electronic case-record form (CRF) was used for data entry.

2.1 | Statistical analysis

Descriptive statistics were used to present the data. Categorical variables were summarized as frequencies and percentages and were analyzed using Pearson's χ^2 test. Continuous variables are summarized using the mean and standard deviation. To evaluate the impact of 25(OH)Vit-D levels (25(OH)Vit-D less than 40 nmol/L and 25(OH) Vit-D greater than 40 nmol/L) on all-cause mortality, we used multivariable logistic regression. The odds ratios (ORs) for in-hospital all-cause mortality status were adjusted for gender, ICU duration of stay and 25(OH)Vit-D levels.

A Cox proportional hazards model was used to determine whether hemoglobin had a significant effect on the hazard of mortality. The level of significance was $p < 0.05$. Statistical analysis were conducted using R statistical packages[9] and SPSS version 27 (SPSS).

3 | RESULTS

A total of 231 study participants were included. Of these, 120 (50.2%) had 25(OH)Vit-D levels that were greater than 40 nmol/L. The remaining 119 (49.8%) had a 25(OH)Vit-D that was less than 40 nmol/L. The mean age of the study population was 49 ± 17 year of which 67% were male. The younger age group was slightly dominant in the group with Vit-D less than 40 nmol/L. The median length of hospitaliztion was 18 [6; 53] days while median duration of ICU stay was 13 [2; 66] days. The length of time spent in ICU was higher in the individuals with a higher level of Vitamin D (>40 nmol/L), 21 [5, 64.5] days, 6 [2.00, 61] days in those with lower levels of Vitamin D (≤40 nmol/L; ($p < 0.040$). During the study period, 17 patients (7.1%) died but there was no difference based on vitamin D level ($p = 0.986$) (Table 1).

Individuals in the lower vitamin D level group had were not significantly different in regard to all-cause in-hospital mortality when compared with individuals with higher Vitamin D levels more than 40 nmol/L (adjusted odds ratio [aOR], 2.03; 95% confidence interval (CI): [0.31–13.61]; $p < 0.448$). Male gender was not significant in terms of all-cause in-hospital (aOR, 2.23; 95% CI: [0.37–15.53]; $p < 0.387$) (Table 2). Kaplan–Meier survival analysis showed no significance based on an alpha of 0.05, $LL = 0.36$, $df = 1$, $p = 0.548$, indicating vitamin D levels was not able to adequately predict the

TABLE 1 Demographics and clinical characteristics of the cohort stratified by vitamin-D levels among patients admitted with SARS-CoV 2

Demographics and clinical characteristics	[ALL] *N = 239*	Vit-D ≤ 40 *N = 119*	Vit-D > 40 *N = 120*	*p* value	*N*
Age (*SD*), years	48.6 ± 16.8	46.2 ± 17.0	50.9 ± 16.4	**0.030**	239
BMI (*SD*), years	28.4 (5.19)	27.8 (4.93)	29.0 (5.44)	0.135	153
Gender: *n* (%)				0.006	239
Female	75 (31.4%)	27 (22.7%)	48 (40.0%)		
Male	164 (68.6%)	92 (77.3%)	72 (60.0%)		
Smoking: *n* (%)				1.000	66
Current smoker	13 (19.7%)	6 (18.2%)	7 (21.2%)		
Ex-smoker	6 (9.09%)	3 (9.09%)	3 (9.09%)		
Never smoked	47 (71.2%)	24 (72.7%)	23 (69.7%)		
Source of transmission: *n* (%)				0.234	238
Community	71 (29.8%)	30 (25.4%)	41 (34.2%)		
Contact	106 (44.5%)	55 (46.6%)	51 (42.5%)		
Healthcare worker	3 (1.26%)	3 (2.54%)	0 (0.00%)		
Hospital acquired	4 (1.68%)	3 (2.54%)	1 (0.83%)		
Imported	54 (22.7%)	27 (22.9%)	27 (22.5%)		
Comorbidities: *n* (%)					
HTN	84 (35.1%)	40 (33.6%)	44 (36.7%)	0.720	239
DM	73 (30.5%)	30 (25.2%)	43 (35.8%)	0.101	239
CVD	11 (4.60%)	5 (4.20%)	6 (5.00%)	1.000	239
Chronic lung disease	18 (7.53%)	6 (5.04%)	12 (10.0%)	0.227	239
Chronic kidney disease	12 (5.02%)	9 (7.56%)	3 (2.50%)	0.135	239
Immunocompromised host	2 (0.84%)	0 (0.00%)	2 (1.67%)	0.498	239
In-hospital outcomes: *n* (%)					
Pneumonia	112 (46.9%)	56 (47.1%)	56 (46.7%)	1.000	239
ARDS	25 (10.5%)	13 (10.9%)	12 (10.0%)	0.982	239
ICU admission, *n* (%)	28 (11.7%)	17 (14.3%)	11 (9.17%)	0.303	239
ICU duration of stay (number of days) IQR	13.0 [2.00–66.3]	6.00 [2.00–61.1]	21.0 [5.25–64.5]	**0.040**	30
Admission to discharge (number of days) IQR	18.0 [5.85–52.8]	18.0 [4.90–58.7]	18.0 [6.92–36.3]	0.723	235
Mortality, *n* (%)	17 (7.11%)	9 (7.56%)	8 (6.67%)	0.986	239

Note: Percentages might not add up to 100% due to rounding off.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CVD, cardiovascular diseases; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *SD*, standard deviation.

hazard of mortality. Kaplan–Meier survival probability plots are included for vitamin D. Each plot represents survival probabilities for each group. A Cox Proportional Hazards model was conducted to determine whether Vitamin_D_Level had a significant effect on the hazard of Mortality. Cox proportional hazards regression coefficients for 25(OH)Vit-D less than 40 nmol/L were not significant, $B = -0.39$, $SE = 0.49$, and HR = 0.74, $p < 0.546$, indicating that at any time, an observation in the 25(OH)Vit-D less than 40 nmol/L is not associated with mortality. The event *B* is 25(OH)Vit-D less than 40 nmol/L (Figure 1).

TABLE 2 Multivariate logistic regression analysis of in-hospital death in the overall study cohort

In hospital mortality		Alive	Dead	Univariate aOR (95% CI, *ap* value)	Multivariate logistic regression aOR (95% CI, *ap* value)
Vit-D Levels	More than 40	112 (93.3)	8 (6.7)	0.87 (0.32–2.36, $p = 0.788$)	2.03 (0.31–13.61, $p = 0.448$)
Gender *n* (%)	Male	150 (91.5)	14 (8.5)	2.24 (0.70–9.94, $p = 0.216$)	2.23 (0.37–15.53, $p = 0.387$)
ICU duration of stay	Mean (*SD*)	9.6 ± 14.2	25.9 ± 19.6	1.08 (1.02–1.20, $p = 0.055$)	1.07 (1.01–1.19, $p = 0.105$)

Note: Percents are row percentages. Multivariable analyses were conducted using logistic regression models utilizing the simultaneous method. The models were adjusted for Vit-D Levels, gender, ICU duration of stay.

Abbreviations: aOR, adjusted odds ratio; *ap* value, adjusted *p* value; CI, confidence interval; ICU, intensive care unit.

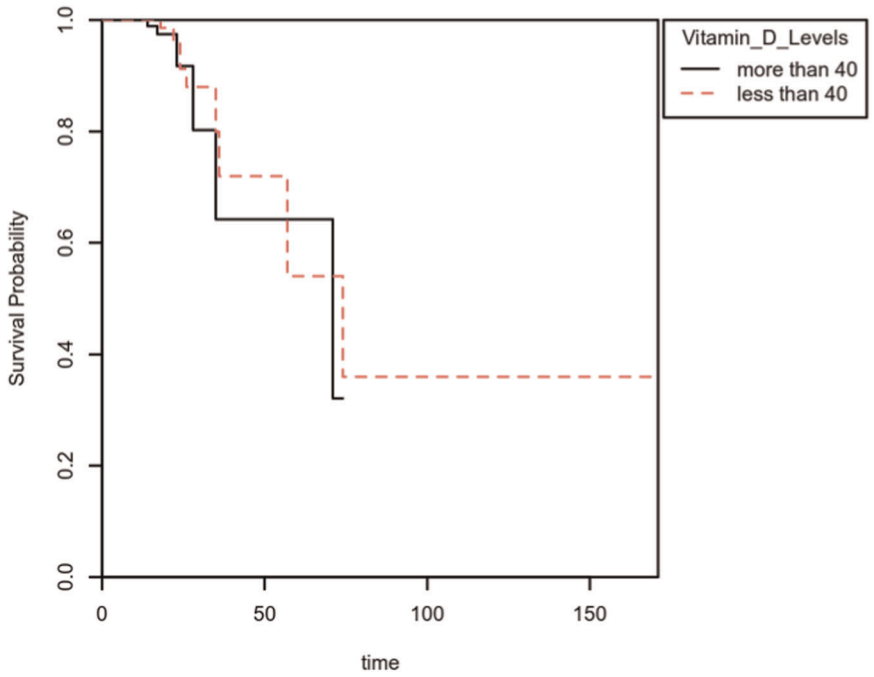

FIGURE 1 Kaplan–Meier survival plot of mortality grouped by Vitamin_D_Levels

4 | DISCUSSION

Our study finds that in individuals with SARS-CoV-2 the level of serum 25(OH)Vit-D levels do not predict in-hospital mortality. Specifically, lower levels of 25(OH)Vit-D levels were not a predictor of increased in-hospital mortality. The average length of ICU stay was longer in the group with higher levels of vitamin D. Groups with vitamin D more than 40 nmol/L were more likely to be elderly patients. Our findings are similar to a study conducted in the UK that showed that Vit-D levels have no impact on SARS-CoV-2 infection.[10] This is one among very few studies like our study which shows no Vit-D levels has a potential role in SARS-CoV-2 infections and related mortality.

Optimal levels of Vit-D are reported to enhance immunity.[11] In SARS-CoV-2 infection and in Vitamin-D deficiency there is an increase in interleukin-6 (IL-6). Many studies have reported increased mortality in individuals with elevated levels of IL-6 and hence lower levels of Vit-D and higher levels of IL-6 may be considered a predictor of poorer prognosis.[12–14] Few studies have reported on the prevalence of Vit-D deficiency in the younger age group.[15] Our study showed that younger age was associated with a lower level of Vit-D (< 40 nmol/L). In another study by Baktash et al.[16] showed lower levels of Vit-D can be a good prognosticator for morbidity especially in elderly age groups. Maintaining the optimal level of Vit-D in SARS-CoV-2 has shown its benefits.[17]

A study conducted in Israel showed more positive cases of SARS-CoV-2 with lower levels of Vit-D and it had an impact on morbidity.[18] In an Austrian study more severe SARS-CoV-2 infection was observed in patients with lower levels of Vit-D.[19] Reduced mortality was seen in a French study especially in the group with SARS-CoV-2 which received Vit-D supplementation.[20] In one study SARS-CoV-2 patients with Vit-D deficiency were more likely to require ICU admission than those with normal values.[21]

A study by Entrenas et al.[22] showed high-dose of Calcifediol was associated with shorter ICU stay and lower mortality in SARS-CoV-2 patients.[10]

A study conducted in the UK showed that Vit-D levels have no impact on SARS-CoV-2 infection.[22]

Our study focused on mortality and thus we did not include other outcome variables. We did not use the cutoff values as defined for Vitamin D deficiency and related classifications.

5 | CONCLUSIONS

Serum 25(OH)Vit-D level was not associated with in-hospital mortality in patients with SARS-CoV-2. Vitamin-D deficiency was more prevalent in younger age groups (Tables 1 and 2).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was approved by the ethics committee and Ministry of Health, Kuwait

AUTHOR CONTRIBUTIONS

Mohammed Al-Jarallah Participated in analysis and manuscript preparation. Rajesh Rajan and Raja Dashti participated in data analysis and manuscript preparation. Ahmad Al Saber and Jiazhu Pan did the statistical analysis as well as manuscript review. All authors had access to data and take responsibility for the integrity of data and the accuracy of data analysis. All authors have read and approved the manuscript.

PATIENT CONSENT STATEMENT

Patient consent was not mandated for this retrospective observational study. Permission to reproduce material from other sources: No material from other sources is included in this study.

CLINICAL TRIAL REGISTRATION

This study was not a clinical trial

NOVELTY STATEMENT

This study mainly focused on the clinical significance of serum 25-Hydroxy-Vitamin D (**25(OH)Vit-D**) levels while treating SAR-CoV-2 infection.

ORCID

Mohammed Al-Jarallah https://orcid.org/0000-0002-8664-2957
Rajesh Rajan http://orcid.org/0000-0002-0249-0440
Raja Dashti https://orcid.org/0000-0002-3775-8478
Ahmad Al Saber https://orcid.org/0000-0001-9478-0404
Jiazhu Pan https://orcid.org/0000-0001-7346-2052
Kobalava D. Zhanna https://orcid.org/0000-0003-1126-4282
Peter A. Brady https://orcid.org/0000-0002-2859-1119
Ibrahim Al-Zakwani http://orcid.org/0000-0002-3626-4230
Moudhi Alroomi http://orcid.org/0000-0001-6907-011X

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