In-hospital Mortality in SARS-CoV-2 stratified by serum 25-Hydroxy-Vitamin D levels: A Retrospective Study

Running Title: Mortality in SARS-CoV-2 stratified by serum 25-Hydroxy-Vitamin D (**25(OH)Vit-D**) levels

Key Words: SARS-CoV-2, COVID-19, In-hospital mortality, Vitamin D

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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.

Highlights:

- This is one among the very few studies which shows serum Vitamin-D levels has no role in predicting the in-hospital mortality in SARS-CoV-2 patients.

In-hospital Mortality in SARS-CoV-2 stratified by serum 25-Hydroxy-Vitamin D levels: A Retrospective Study

Abstract

This study is to estimate in-hospital mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients 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, i.e., 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 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 SARS-CoV-2 patients.

Key Words: SARS-CoV-2, COVID-19, In-hospital mortality, Vitamin D

Introduction

Serum Vitamin D levels in SARS-CoV-2 range between 23% to 80%. [1,2] Lower levels of Vitamin D were associated with 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 viitamin D levels 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]

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 RT-PCR 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 level less than 50 nmol/L were considered Vitamin-D deficency, 50-72 nmol/L as Vitamin-D insufficiency and levels more than 75 nmol/L were considered normal. [8]

The primary outcome measured was COVID-19-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 ICU and in-hospital stay. An electronic case-record form (CRF) was used for data entry.

Statistical Analysis

Descriptive statistics were used to present the data. Categorical variables were summarized as frequencies and percentages and were analyzed using Pearson's X^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, Chicago, IL, USA).

Results

A total of 231study 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 were slightly dominated in the group with Vit-D less than 40nmol/L. The median length of hospitaliztion was 18 [6; 53] days while median duration of intensive care unit (ICU) stay was 13 [2; 66] days. The length time spent in ICU was higher in the individuals with higher level of Vitamin D (more than 40 nmol/L), 21 [5, 64.5] days, 6 [2.00, 61] days in those with lower levels of Vitamin D (less than or equal to 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 regards to all-cause in-hospital mortality when compared with individuals with higher Vitamin D levels > 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 interms of all-cause in-hospital (adjusted odds ratio (aOR), 2.23; 95% confidence interval (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 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]

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. Group with Vitamin D more than 40nmol/L were more likely to be elderly patients. Our findings are similar to a study conducted in United Kingdom showed that Vit-D levels has no impact in SARS-CoV-2 infection. [25] This is one among very few studies like our study which shows no Vit-D levels has potential role in SARS-CoV-2 infections and related mortality

Optimal levels of Vit-D are reported to enhance immunity [10] In SARS-CoV-2 infection and in Vitamin-D deficiency there is an increase in interlukin-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. [11,12,13]. Few studies have reported on the prevalence of Vit-D deficency in younger age group. [14] Our study showed that younger age was associated with a lower level of Vit-D (< 40nmol/L). In another study by V.Baktash et.al showed lower levels of Vit-D can be a good prognosticator for mobidity especially in elderly age groups. [15] Maintaining the optimal level of Vit-D in SARS-CoV-2 has shown its benefits. [16]

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. [17] In an Austrian study more severe SARS-CoV-2 infection was observed in patients with lower levels of Vit-D. [18] Reduced mortality was seen in a French study especially the group with SARS-

CoV-2 which received Vit-D supplementation. [19] In one study SARS-CoV-2 patients with Vit-D deficiency were more likely to require ICU admission than those with normal values. [20]

A study by Entrenas et.al showed high-dose of Calcifediol was associated with shorter ICU stay and lower mortality in SARS-CoV-2 patients. [21]

A study conducted in United Kingdom showed that Vit-D levels has no impact in 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.

Conclusions

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

Abbrevations :

25(OH)Vit-D = 25-Hydroxy-Vitamin D
aOR = adjusted Odds Ratio
CI = Confidence Interval
CRF = Case Record Form
ICU = Intensive Care Unit
RT-PCR = Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Author's contributions :

MAJ participated in analysis and manuscript preparation. RR & RD participated in data analysis and manuscript preparation. AAS and JP 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.

Conflict of interest disclosure: No conflict of interest exists for any author on this manuscript.

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