RESEARCH LETTER

Moderate to severe vitamin D deficiency increases the risk of mortality due to COVID-19 in patients treated in a respiratory intensive care unit

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Introduction The association between vitamin D insufficiency and increased risk of respiratory tract infection has been widely discussed before the COVID-19 pandemic.[1-3] Interestingly, the relation between vitamin D status and viral infections is still unknown. It has been suggested that vitamin D may lower the risk of SARS-CoV-2 infection and death by multiple mechanisms of action.[4]

In a recent investigation performed during the first wave of the pandemic, our group showed that COVID-19 patients admitted to a respiratory intensive care unit (RICU) with severe vitamin D deficiency had a significantly higher mortality risk.[5] Since the level of solar ultraviolet radiation is higher in areas nearest to the equator, it may be expected that vitamin D levels peak after the summer, particularly in people living in southern Italian regions. A correlation between country latitude and COVID-19 mortality has been documented.[6] Hence, this study aimed to extend our previous observations and to assess the impact of vitamin D levels on COVID-19–related in-hospital death rates within patients admitted to an RICU during the first and second waves of the COVID-19 pandemic, which occurred before and immediately after the summer of 2020, respectively.

Patients and methods A total of 83 patients with COVID-19 were enrolled in the this retrospective, observational, single-center study. They were admitted to the RICU of the University Hospital Policlinico, Bari, Italy, during 2 periods, matching the first and second waves of the pandemic: from March 1, 2020 to April 30, 2020 and from September 1, 2020 to November 15, 2020.

Data were collected by the physicians of the unit. The study was approved by the local ethics committee (protocol number 6380) and all patients provided written informed consent to participate.

COVID-19 diagnosis was established according to the World Health Organization interim guidance.[7] A confirmed case of COVID-19 was defined as a positive result for SARS-CoV-2 by high-throughput sequencing or a real-time reverse transcriptase–polymerase chain reaction assay of nasal and pharyngeal swab specimens. Laboratory-confirmed cases with acute respiratory failure not requiring intubation or invasive ventilation in an intensive care unit (ICU) were also hospitalized in the RICU and were included in the present analysis.

Serum 25-hydroxyvitamin D concentrations were measured using chemiluminescence immunoassay (Technogenetics, Lodi, Italy). Vitamin D insufficiency, moderate deficiency, and severe deficiency were defined as 25-hydroxyvitamin D levels of 20–29 ng/ml, 10–19 ng/ml, and <10 ng/ml, respectively.[8] Subsequently, the study group was divided into 2 subgroups according to their blood levels of vitamin D: Group 1, with moderate to severe vitamin D deficiency (<20 ng/ml) and Group 2, with vitamin D values equal to or greater than 20 ng/ml.

The medical history as well as data on demographics, comorbidities, symptoms, and signs of disease were collected from all participants within the first 12 hours following their admission to the RICU. We also gathered information about laboratory findings, respiratory parameters such as the fraction of inspired oxygen and

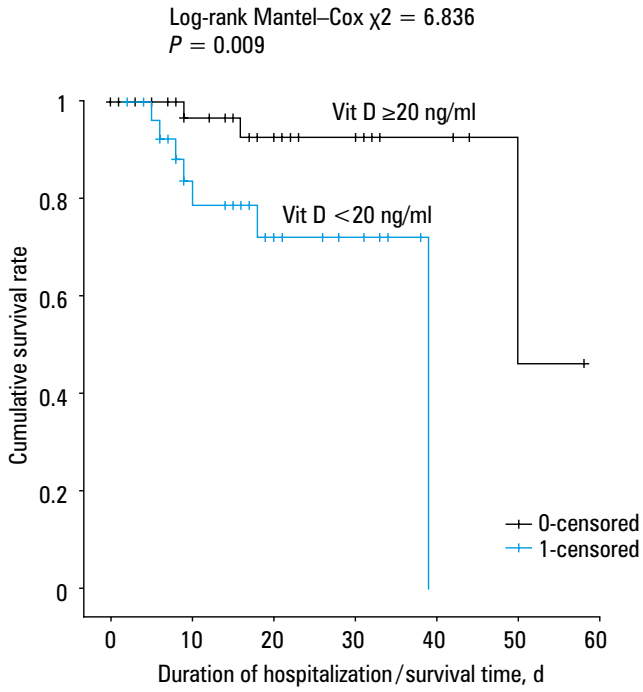

FIGURE 1 Survival analysis in patients with vitamin D (Vit D) levels below 20 ng/ml and those with vitamin D levels of 20 ng/ml or higher

the ratio of arterial partial pressure oxygen to fraction of the inspired oxygen, respiratory and pharmacological treatments, and outcomes of all patients.

Statistical analysis All data were analyzed by statistical software IBM SPSS Statistics 23.0 for Windows (Chicago, Illinois, United States). Continuous variables were expressed as mean (SD) or median (interquartile range) depending on whether they followed a normal or nonnormal distribution. Dichotomous or noncontinuous variables were expressed as percentage. We confirmed that all quantitative variables followed a normal distribution using the 1-sample Kolmogorov–Smirnov test.

The independent subgroups of continuous variables were compared with the Mann–Whitney test, whereas the χ^2 test was used to compare categorical variables.

Two Kaplan–Meier curves were compared with the log-rank test. Consequently, Cox proportional hazards analysis was performed, and the significant results were inserted into the multivariate Cox model. The accuracy of this model was then calculated by constructing a receiver operating characteristic curve. Results of the Cox regression model were presented as hazard ratios (HRs) and 95% CIs. A *P* value of less than 0.05 was considered significant.

Results and discussion Men constituted 73.5% of the study population. The mean (SD) age of patients was 65.4 (11.9) years, and the median (interquartile range) level of vitamin D was 18.00 (12.00–25.00) ng/ml. There were 30 patients with moderate to severe vitamin D deficiency (<20 ng/ml; Group 1) and 83 individuals with vitamin D levels of 20 ng/ml or higher (Group 2).

Compared with patients in Group 2, those in Group 1 had higher BMI values (29.39 [24.86–35.86] vs 24.95 [23.17–30.74]; *P* = 0.02) and slightly higher values of international normalized ratio (1.19 [1.14–1.19] vs 1.10 [1.03–1.15]; *P* = 0.01). There were also fewer women in Group 1 (13.3% vs 34%; *P* = 0.03). Furthermore, it was found that values of vitamin D below 20 ng/ml were associated with a higher rate of in-hospital death (23.3% vs 5.7%; *P* = 0.02).

Kaplan–Meier analysis showed that patients with moderate to severe vitamin D deficiency had reduced survival (log-rank Mantel–Cox χ^2 = 6.8; *P* = 0.009) (FIGURE 1).

In univariate Cox regression it was showed that vitamin D values below 20 ng/ml on admission were a risk factor for in-hospital mortality (HR, 6.37; 95% CI, 1.30–31.15; *P* = 0.02). Other identified risk factors were age (HR, 1.085; 95% CI, 1.02–1.15; *P* = 0.006), pre-existence of interstitial disease (HR, 12.98; 95% CI, 1.45–116.43; *P* = 0.02), lymphocytopenia (HR, 0.13; 95% CI, 0.02–0.98; *P* = 0.04), and high blood levels of creatinine (HR, 1.64; 95% CI, 1.12–2.38; *P* = 0.01).

Significant predictors from univariate analysis were used to build a multivariate Cox model. Interestingly, only lymphocytes on admission lost their significance (HR, 0.06; 95% CI, 0.002–2.26; *P* = 0.12), whereas the predictive capacity of vitamin D values below 20 ng/ml increased, with HR of 30.13 (95% CI, 2.43–372.9; *P* = 0.008) as compared with the HR of 6.37 of the univariate analysis. Similarly, blood levels of creatinine on admission (HR, 42.09; 95% CI, 1.45–1222.5; *P* = 0.02) and the pre-existence of interstitial disease (HR, 42.09; 95% CI, 1.45–1222.5; *P* = 0.03) enhanced their predictive ability. Our data are in line with the recent observations by Yao et al,[9] who evaluated risk factors for severe acute respiratory syndrome in hospitalized adult patients with SARS-CoV-2 infection.

To verify the accuracy of the model above, a receiver operating characteristic curve was constructed, with the area under the curve of 0.97 (95% CI, 0.94–1.00; *P* <0.001).

The present study demonstrated that patients with moderate to severe vitamin D deficiency (<20 ng/ml) have a higher risk for in-hospital mortality due to COVID-19 than those with higher levels of vitamin D. Our results are in line with previous studies which reported a strong relation between vitamin D deficiency and ICU admission, pulmonary complications, hospitalization, and inflammation.[5,10-12] Indeed, we previously showed that during the first wave of the COVID-19 pandemic from March to June 2020, the rate of death after 10 days of hospitalization was increased in patients with severe vitamin D deficiency (<10 ng/ml).[5] However, despite a long summer with high temperatures and increased opportunity for exposure to sunlight, a large percentage of patients admitted during the second wave still had

vitamin D hypovitaminosis (vitamin D <30 ng/ml; 81% vs 61.4% of patients admitted during the first and second waves, respectively).

In the present study, we did not identify significant differences in serum levels of inflammatory markers in the 2 groups. This was confirmed in multivariate Cox regression analysis. Nevertheless, our study patients had severe acute respiratory failure requiring prone positioning and respiratory support, and they were burdened by multiple respiratory complications.[13,14] Thus, the insult driven by the virus may have caused an acute inflammatory response. For this reason, we speculate that vitamin D levels may be linked to the outcomes of patients with COVID-19 irrespective of their general inflammatory status.

We must underline the relation between vitamin D levels and sex and BMI. It is noteworthy that patients with moderate to severe vitamin D deficiency were more frequently male and had higher BMI values. Indeed, male sex and obesity were associated with increased mortality in all patients with COVID-19.[15] Our data also showed that lower blood levels of creatinine as well as pre-existent interstitial lung diseases may be predictors of a negative outcome. However, our sample size was not sufficient to find significant differences in creatinine levels between the 2 groups. The possible association between serum vitamin D levels, chronic kidney disease, and clinical outcomes in patients with COVID-19 warrants further studies on larger populations.

This study has some limitations. First, the relatively small sample size might have limited the statistical power. Second, we lacked data about pneumonia severity (eg, pneumonia severity index/PORT score), which are necessary for future investigations. Third, although data were collected over 2 different periods before and after the summer, we could not explore possible differences in terms of sun exposure.

In conclusion, our study demonstrated that moderate to severe vitamin D hypovitaminosis may predict worse prognosis and increased in-hospital mortality in patients with severe COVID-19 and acute respiratory failure. Further clinical studies with larger populations are required to elucidate the possible role of vitamin D supplementation as a supportive treatment of COVID-19.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The datasets generated and/or analyzed in the present study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST None declared.

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