RESEARCH LETTER

Patients hospitalized with COVID-19 have low levels of 25-hydroxyvitamin D

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The coronavirus (SARS-CoV-2) causes COVID-19. The disease has already afflicted over 54 million persons worldwide and has caused over 1.3 million deaths [1]. While most patients recovery uneventfully, some develop an acute pulmonary syndrome that requires hospitalization for supportive care [2]. Risk factors for symptomatic manifestations include male sex, diabetes mellitus, obesity, and hypertension [3, 4]. Another recently recognized potential risk factor is vitamin D deficiency. Vitamin D is an important modulator of innate and acquired immunity [5, 6]. Low levels are associated with bacterial and viral infections [7]. In addition, in countries with lower mean levels of 25-hydroxyvitamin D, mortality from COVID-19 is higher [8]. Preliminary studies suggest that vitamin D supplementation may improve outcomes [9]. While much of the data implicating vitamin D and COVID-19 has been indirect, recent reports have shown markedly reduced levels of 25-hydroxyvitamin D among those hospitalized with COVID-19 [10, 11]. These observations are consistent with

a plausible pathophysiological role of vitamin D in the disease process [6].

With an ethnically and culturally homogeneous population of approximately 3 million [12], Armenia has seen ~116,000 cases and 1700 deaths as of November 2020 [13]. At the Saint Gregory the Illuminator Medical Center (SGIMC) in Yerevan, a designated COVID-19 treatment hospital, we measured levels of 25-hydroxyvitamin D. We compared these levels with values that we have recently characterized in the free-living, healthy population of Armenia [14].

Methods

Blood samples for measurement of 25-hydroxyvitamin D (ElectroChemiLuminescence immunoassay: Cobas e 411 autoanalyzer- Roche; Basel, Switzerland) were obtained from 330 consecutive hospitalized patients. We also recorded age, gender, height, weight, occupation, chronic conditions, prior tuberculosis infection, smoking status, use of supplemental oxygen, intubation status, duration of hospitalization until discharge, or death.

Results

Samples were collected over 5 weeks in summer, 2020. The most common comorbidities were hypertension, diabetes, smoking, and prior lung disease. Mean duration of hospitalization was 11 ± 7.4 days. A majority (52%) required supplemental oxygen but only 4.5% were intubated. There were 24 deaths (7.3%). Mean 25-hydroxyvitamin D level was 13.4 ± 7.7 ng/mL, with 45% of patients under 12 ng/mL. See Table 1.

Positive relationships were noted between age and the duration of hospitalization, age and days on supplemental oxygen, BMI and days hospitalized, BMI with days on

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Table 1 Demographic and clinical characteristics, and laboratory findings of patients hospitalized with COVID-19

Patient count	330
Gender	39% male
Mean age	57 ± 17 years
Mean BMI	$28.2 \pm 5.8 \text{ kg/m}^2$
Comorbidities	Hypertension (27.5%)
	Diabetes (16%)
	Smoking (11.5%)
	Lung disease (7.3%)
Hospital stay	11 ± 7.4 days
Use of supplemental oxygen	171 patients (52%)
Intubation	15 patients (4.5%)
Death	24 (7.3%)
Mean 25-hydroxyvitamin D	13.4 ± 7.7 ng/mL
25-hydroxyvitamin D < 12 ng/mL	149 (45%)

supplemental oxygen, and number of comorbidities with days on supplemental oxygen. In addition, multivariate logistic regression identified age and duration of hospitalization and significant variables for death. There was no relationship between any of the demographic variables and intubation.

We found no significant relationship between 25-hydroxyvitamin D and BMI, duration of stay, oxygen requirements, or death. The mean level of 13.4 ± 7.7 ng/mL was markedly lower than the mean 25-hydroxyvitamin D level among women in Armenia of 19.8 ± 7.6 ng/m ($p < 0.0001$). Mean vitamin D of those patients who passed away was mildly lower than that of those who survived, however the difference was not significant (11.69 ng/mL vs 13.51 ng/mL, $p = 0.27$). A greater proportion of hospitalized patients had levels below 12 ng/mL in comparison to the national average, but in comparing those with vitamin D levels below 12 ng/mL to those with vitamin D levels above 12 ng/mL, we found no difference in terms of mean age, BMI, duration of hospitalization, or days requiring supplemental oxygen.

Discussion

The results of this report support a potential role for vitamin D as a risk factor for COVID-19, as suggested recently in studies from Italy and Spain [11, 15]. It also adds clinical strength to much basic information implicating vitamin D in the native and acquired immune response.

An additional strength of this study is the newly acquired reference data on healthy subjects' 25-hydroxyvitamin levels in Armenia with which these significantly lower levels could be compared [14]. What is also noteworthy is the very low levels of 25-hydroxyvitamin D, below 12 ng/mL, a threshold value acknowledged by all authoritative

bodies to be associated with frank, unequivocal vitamin D deficiency. Almost half the infected population was below this value, a markedly greater percentage than in our reference population in which such low levels were seen in only 13%. Such very low levels could have devastating effects upon the host's ability to contain the acquired immune response as well as bolster its cellular defense mechanisms.

Additional strengths of this study include the size of the patient cohort and the homogeneity of the cohort which reduces the influence of cultural, ethic, or lifestyle on disease severity. Limitations include the lack of a pre-SARS-CoV-2 infection 25-hydroxyvitamin D level in the individual patients. In addition, we do not know the extent to which the acute illness itself might have influenced the level of vitamin D or vitamin D binding protein, the latter of which we did not measure.

It is important to conduct prospective studies to determine if intervention with vitamin D can be protective against COVID-19 as well as whether intervention with vitamin D can mitigate its severity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Columbia University Irving Medical Center, and the Ethics Committee of the Yerevan State Medical University.

Informed consent Both review boards waived informed consent as a requirement because the study entailed analysis of previously collected and de-identified data.

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