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# Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy, Italy

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## Introduction

Recent literature has substantially raised interest in the immune-modulating properties of vitamin D against coronavirus disease 2019 (COVID-19). Although several viewpoints have been published, data supporting the hypothesized beneficial role are limited and controversial [1,2]. Consistent with a systematic review reporting the protective role of 25-hydroxyvitamin D (25OHD) supplementation [3], in a recent survey conducted in individuals with Parkinson disease (PD), those with COVID-19 were more likely not to be taking supplements than participants who were unaffected [4]. The observation of lower mortality rates at lower degrees of latitude, along with other preliminary reports on the association between serum levels of 25OHD and the risk of having the disease or a critical outcome, have suggested that vitamin D could modulate the risk and mitigate the severity of COVID-19 [1,2,5]. There is evidence that vitamin D has immunomodulatory functions and plays an antiinflammatory role, particularly in viral infections. It has also been demonstrated to be inversely correlated to acute respiratory distress syndrome and increased levels of C-reactive protein [6]. On the other hand, the higher prevalence of 25OHD deficiency in many disease conditions is questionable according to a reversed causality hypothesis, as the underlying disease and related inflammatory background may negatively influence 25OHD metabolism, particularly that of its binding protein, resulting in substantial bias in the assessment of its status [7,8]. This is also suggested by differences in serum levels between those who are positive and negative on polymerase chain reaction tests, which might not only be interpreted as a higher susceptibility to infection in those with deficiency status [5,9]. Therefore, we aimed to evaluate whether 25OHD supplementation, which may be a better surrogate of real 25OHD status, is associated with prognosis in COVID-19 patients from the Italian outbreak area of Lombardy.

### Methods

The study was approved by local institutional ethics committees, and written informed consent was obtained from every participant.

Two sets of data collected prospectively during the outbreak of the pandemic in the north of Italy were pooled and analyzed. The first consisted of COVID-19 PD patients (group 1) and COVID-19 PD caregivers (group 2) identified from a pool of

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2693 PD patients ($n$ = 1486) and caregivers ($n$ = 1207) who were approached in a recent phone survey and interview conducted between March and May 2020 [4]. The second comprised consecutive COVID-19 patients (group 3) admitted to a referral hospital between April and May 2020 (unpublished data). Information on supplementation with 25OHD (defined as at least 25 000 IU/mo in the last 3 mo, ~800 IU/d), weight status, comorbidities, serum 25OHD, COVID-19 diagnosis, and related hospitalization and in-hospital mortality were gathered by direct interview and validated through the consultation of institutional electronic charts and linkage to the regional register of health care data. In hospital inpatient participants, fasting venous serum samples were collected within 48 h of admission for the assessment of 25OHD (chemiluminescence immunoassay; Abbott Diagnostics, Lake Forest, IL, USA). Hospitalization and in-hospital mortality for COVID-19 were the study end points.

Analyses were conducted using Stata 16 (StataCorp, College Station, TX, USA). Comparisons (supplemented versus non-supplemented) of continuous variables were performed using parametric or non-parametric tests, while categorical variables were analyzed by the Fisher's exact test. Then adjusted logistic regression was used to investigate the association between supplementation and study outcomes.

## Results

Overall, 324 COVID-19 cases were included: 105 in group 1 (PD patients), 92 in group 2 (PD caregivers), and 127 in group 3 (hospital inpatients). The characteristics of the study participants are summarized in Table 1. The use of 25OHD supplements (mean intake, 58.846 IU/mo) was reported by 38 (11.7%) participants out of 324. Clinical and demographic features of supplement users and non-users were comparable. Serum 25OHD levels of supplemented inpatients ($n$ = 11) were about 3-fold higher than those of non-users. However, among these participants, two had insufficient levels (20–30 ng/mL; range, 24.7–29.4 ng/mL) and three presented a deficiency status (<20 ng/mL; range, 18.0–19.7 ng/mL). Forty-three (21.8%) out of 197 participants with COVID-19 identified through the phone survey required hospitalization, and 47 (27.6%) of hospitalized patients ($n$ = 170) died. The use of 25OHD supplements was not associated with either hospitalization or in-hospital mortality, although a trend toward a 2-fold higher risk of death was found for supplement users, particularly after adjusting for potential confounders (Table 2).

## Discussion

In our study, 25OHD supplementation was not associated with the severity of COVID-19. On the other hand, a trend toward a 2-fold higher mortality in users was found.

Vitamin D could boost mucosal defenses and protect against infections [1–6], and it has been suggested to down-regulate the inflammatory burden contributing to acute respiratory distress syndrome and lung injury [2,10,11], the main cause of death in COVID-19 patients. Enhanced ACE2 expression is considered a protective factor in acute lung injury [10,11]. Vitamin D increases the expression of ACE2 [6], and this may apply not only to airway epithelium but also to other organs and monocyte-derived macrophages. However, ACE2 is the binding site of SARS-CoV-2, and increased ACE2 expression may result in enhanced viral homing and organ damage, as well as in an aberrant innate immune response with hyperactivation of macrophages [11]—perhaps at least in patients with high complication, such as those admitted in our outbreak area.

Our data may appear in contrast with recent literature suggesting that higher serum 25OHD is associated with more favorable COVID-19 outcomes, with lower progression of respiratory illness and to critical illness, as well as lower mortality rates [1,2,5,12], although no association has been also reported [13]. However, disease-related inflammation may negatively affect 25OHD metabolism, particularly that of its binding protein, resulting in reduced circulating levels and assessment bias [7,8]. From this perspective, the timing of assessment in relation to the onset of symptoms could also play a role [13]. It is with this background that we decided to evaluate the association between supplementation rather than serum levels and outcome. Nonetheless, we evaluated serum 25OHD in a subgroup of consecutive patients, demonstrating that supplementation results in substantially higher and adequate circulating levels.

Therefore, although the potential utility of vitamin D in the prevention of respiratory-tract infections is more substantial [3], its benefits in COVID-19 (prevention and management) still need to be clarified by appropriate intervention trials.

We recognize the following limitations. First, a larger study population, along with multicenter participation, would have resulted in increased statistical power and bias reduction. However, we were not able to perform a valid calculation of the sample size, due to the emergency crisis and the heterogeneity in published data on outcomes and use of supplements. Indeed, we recognize that the emergency crisis was a source of bias itself, as it is likely that only individuals with the worst cases were hospitalized in our outbreak area. Finally, in agreement with Italian recommended dietary

**Table 1**
Main demographic and clinical features of COVID-19 patients by setting and vitamin D supplementation

| Characteristic | Group 1 (PD patients, $n$ = 105) | Group 2 (caregivers of PD patients, $n$ = 92) | Group 3 (hospital inpatients, $n$ = 127) | Supplemented ($n$ = 38) | Non-supplemented ($n$ = 286) | $P$* |
|---|---|---|---|---|---|---|
| Male sex, $n$ (%) | 55 (52.4) | 44 (47.8) | 58 (45.7) | 16 (42.1) | 141 (49.3) | 0.49 |
| Age, y, mean (SD) | 70.5 (10.1) | 65.4 (11.0) | 73.5 (14.7) | 68.8 (10.6) | 70.5 (13.1) | 0.39 |
| Body mass index, kg/m$^2$, mean (SD) | 25.6 (4.9) | 25.2 (4.4) | 25.1 (4.5) | 25.1 (4.5) | 25.4 (4.4) | 0.74 |
| Obesity, $n$ (%) | 19 (18.1) | 13 (14.1) | 14 (11.0) | 5 (13.2) | 41 (14.3) | 0.99 |
| Comorbidities, $n$, mean (SD) | 1.6 (0.7)† | 0.9 (0.8) | 1.9 (1.3) | 1.5 (1.2) | 1.5 (1.1) | 0.92 |
| Ischemic heart disease, $n$ (%) | 5 (4.8) | 5 (5.4) | 51 (40.2) | 8 (21.1) | 53 (18.5) | 0.66 |
| Hypertension, $n$ (%) | 44 (41.9) | 51 (55.4) | 87 (68.5) | 20 (52.6) | 162 (56.6) | 0.73 |
| Diabetes, $n$ (%) | 8 (7.6) | 11 (12.0) | 38 (29.9) | 6 (15.8) | 51 (17.8) | 1.00 |
| COPD, $n$ (%) | 6 (5.7) | 8 (8.7) | 15 (11.8) | 2 (5.3) | 27 (9.4) | 0.55 |
| Cancer, $n$ (%) | 1 (0.9) | 2 (2.2) | 26 (20.5) | 6 (15.8) | 20 (7.0) | 0.10 |
| PD, $n$ (%) | 105 (100) | 0 (0) | 1 (0.1) | 13 (34.2) | 93 (32.5) | 0.86 |
| Vitamin D supplementation, $n$ (%) | 13 (12.4) | 14 (15.2) | 11 (8.7) | — | — | — |
| Serum 25OHD, ng/mL, mean (SD)‡ | — | — | 13.2 (11.1) | 32.9 (14.8) | 11.3 (8.6) | <0.001 |
| Hospitalization, $n$ (%) | 18 (17.1) | 25 (27.2) | — | — | — | — |
| In-hospital mortality, $n$ (%)§ | 6 (33.3) | 7 (28.0) | 34 (26.8) | See Table 2 | | |

25OHD, 25-hydroxyvitamin D; COPD, chronic obstructive pulmonary disease; PD, Parkinson disease; SD, standard deviation.
*Supplemented versus non-supplemented according to the unpaired Student's $t$ test (continuous variables) or the Fisher's exact test (categorical variables).
†Including PD.
‡In hospital inpatients only.
§In-hospital mortality (%) has been calculated according to the number of hospitalized patients.

**Table 2**
Association between vitamin D supplementation and outcomes (logistic regression)

| Outcome | Case population, *n* | 25OHD supplemented | | 25OHD non-supplemented | | OR (95% CI)* | *P* | Adjusted OR (95% CI)* | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | | Patients, *n* | Events, *n* (%) | Patients, *n* | Events, *n* (%) | | | | |
| Hospitalization | 197 | 27 | 7 (25.9) | 170 | 36 (21.2) | 1.30 (0.51–3.32) | 0.56 | 1.25 (0.46–3.35)† | 0.66 |
| | | | | | | | | 1.23 (0.46–3.27)‡ | 0.68 |
| In-hospital mortality | 170 | 18 | 7 (38.9) | 152 | 40 (26.3) | 1.78 (0.64–4.91) | 0.26 | 2.42 (0.78–7.49)† | 0.13 |
| | | | | | | | | 2.34 (0.76–7.21)‡ | 0.14 |

25OHD, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
*ORs are provided for the supplemented group (reference category: non-supplemented group, OR = 1).
†Adjusted for age, sex, body mass index, PD, and number of other comorbidities.
‡Adjusted for age, sex, body mass index, PD, and ischemic heart disease (the only comorbidity associated with mortality in univariate analysis).

allowances [14], we decided to define supplementation as an intake of at least 25 000 IU/mo (~800 IU/d) in the previous 3 mo. It is not at all clear that supplements of <1000 IU/d are likely to make much difference compared with larger ones. However, the mean intake for participants taking supplements was >54000 IU/mo (>1800 IU/d), resulting in adequate circulating levels in most participants assessed.

In conclusion, 25OHD supplementation was not associated with hospitalization but appeared to be a risk factor for higher in-hospital mortality in COVID-19. Further studies are needed to clarify the role of vitamin D supplementation and status in modulating the severity of COVID-19, as well as preventing it.

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