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Vitamin D supplementation prior to or during COVID-19 associated with better 3-month survival in geriatric patients: Extension phase of the GERIA-COVID study

Short title: Vitamin D and COVID-19

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ABSTRACT

Background. The objective of this extension phase of the quasi-experimental GERIA-COVID study was to determine whether vitamin D3 supplementation taken prior to or during COVID-19 was associated with better 3-month survival in geriatric patients hospitalized for COVID-19.

Methods. Intervention group was defined as all participants supplemented with vitamin D3 prior to or during COVID-19 (n=67). Supplements were either bolus vitamin D3 (ie, 50,000IU per month, or 80,000IU or 100,000IU or 200,000IU every 2-3 months), or daily supplementation with 800IU. Comparator group involved those without vitamin D supplements (n=28). Outcome was 3-month mortality. Covariables were age, sex, functional abilities, history of malignancies, cardiomyopathy, undernutrition, number of acute health issues, antibiotics use, systemic corticosteroids use, and 25(OH)D concentration.

Results. 76.1% (n=51) of participants survived at 3 months in Intervention group, compared to only 53.6% (n=15) in Comparator group (P=0.03). The fully-adjusted hazard ratio for 3-month mortality was HR=0.23[95%CI:0.09;0.58](P=0.002) in Intervention group compared to Comparator group. Intervention group had also longer survival time (log-rank P=0.008).

Conclusions. Vitamin D3 supplementation was associated with better 3-month survival in older COVID-19 patients.

Keywords: vitamin D; COVID-19; SARS-CoV-2; treatment; epidemiology; older adults

1. INTRODUCTION

The COVID-19 caused by SARS-CoV-2 spreads worldwide, affecting millions of people and causing hundreds of thousands deaths, notably in older adults. With the lack of effective therapy and the emergence of immune-escape variants (1), the search for a treatment in parallel with the vaccine efforts remains crucial and focusing on the repurposing of existing drugs gives hope of curbing the pandemic. Importantly, an *in-silico* study has identified vitamin D among the three molecules most likely to attenuate the effects of COVID-19 through its effects on gene expression (2). Consistently, we previously reported in a quasi-experimental study among frail elderly hospitalized for COVID-19 that the use of vitamin D3 supplements was associated with less severe COVID-19 and better survival at day 14 (3). Such follow-up made it possible to include the mortality risk linked to the cytokine storm generally occurring between 7 and 10 days of the SARS-CoV-2 infection (1). However, recent data shows that COVID-19 may also have medium and long-term consequences on morbidity and mortality that go beyond the acute stage of the infection (4). In this perspective, finding a treatment capable of improving the vital prognosis in the short but also in the longer term appears crucial. We had the opportunity to follow the GERIA-COVID participants beyond their hospitalization for up to 3 months. Since bolus vitamin D3 supplementation improves vitamin D status for weeks (5) and given the short-term improvement in survival observed in COVID-19 patients under vitamin D3 supplementation (3,6), we hypothesized that vitamin D3 supplementation could be effective in improving 3-month survival in geriatric patients with COVID-19. The main objective of this extension phase of the quasi-experimental GERIA-COVID study was to determine whether vitamin D3 supplementation

taken either prior to or during COVID-19 was associated with better 3-month survival among geriatric COVID-19 patients.

2. MATERIALS AND METHODS

2.1 Participants

We studied all consecutive participants enrolled during the first wave of the pandemic (between March and June 2020) in the quasi-experimental GERIA-COVID study within the geriatric acute care unit of the University Hospital of Angers, France (3). A first analysis of 14-day mortality was previously published on a subsample of this cohort (the patients included between March and May 2020, at the time of writing the first report)(3). Inclusion criteria for the present analysis were as follows: 1) COVID-19 diagnosed with RT-PCR and/or chest CT-scan; 2) data available on the serum measures and on the usual treatments; 3) vital status available 3 months after the diagnosis of COVID-19.

Ninety-seven patients with COVID-19 were consecutively admitted into the unit during the study period and recruited in the GERIA-COVID study. Among them, 2 participants had missing values of serum albumin and 25-hydroxyvitamin D (25(OH)D) concentrations. Finally, 95 participants were included in the present analysis.

2.2 Intervention: vitamin D3 supplementation

The Intervention group was defined as all COVID-19 participants who had orally received vitamin D3 supplements either prior to hospitalization (systematically noted from the primary care physicians' prescriptions and/or sought by questioning the patients and their relatives) and/or during hospitalization and/or at hospital discharge. Bolus included either 50,000 IU vitamin D3 per month, or 80,000 IU or 100,000 IU or 200,000 IU vitamin D3 every 2-3 months. One patient was supplemented with 800 IU vitamin D3 per day. None received D2 or intramuscular supplements.

The Comparator group was defined as all COVID-19 participants who had not received any vitamin D supplements prior to or following the diagnosis of COVID-19; the absence of vitamin D treatment being mostly explained by the patients' refusal to be supplemented.

2.3 Main outcome: 3-month all-cause mortality

The primary outcome was the 3-month all-cause mortality. Follow-up started from the day of COVID-19 diagnosis for each patient and continued for 3 months or until death when applicable. Vital status was recovered by contacting the patients and their relatives by telephone, and by monitoring the National Institute of Statistics and Economic Studies (INSEE) register (https://www.insee.fr/fr/information/4190491).

2.4 Covariables

Potential confounders were age, sex, functioning, severe undernutrition, history of malignancies, cardiomyopathy, number of acute health issues on hospital admission, hospital use of antibiotics, of systemic corticosteroids, and serum 25(OH)D concentration at the time of COVID-19 diagnosis. Functioning prior to COVID-19 was measured from 1 (worst) to 6 (best) with the Iso-Resources Groups (GIR) (7). Serum albumin and 25(OH)D concentrations were measured concomitantly with the diagnosis of COVID-19. Severe undernutrition was defined as albumin < 30g/L. Serum 25(OH)D concentration was measured by immunoanalysis on the automated LIAISON platform (DiaSorin Inc., Saluggia, IT) in nmol/L (to convert to ng/mL, divide by 2.496). Acute health issues were defined as diseases with sudden onset and rapid progression, whatever their nature or site (3). History of hematological and solid malignancies and of cardiomyopathy was noted from the medical register, and by interviewing patients, family physicians and relatives. The use of systemic corticosteroids

and/or antibiotics (i.e., quinolones, beta-lactams, sulfonamides, macrolides, lincosamides, aminoglycosides, among others) was noted from prescriptions during hospitalization.

2.5 Statistical analysis

Participants' characteristics were appropriately summarized using means and standard deviations (SD) or numbers and percentages. Firstly, comparisons according to the study groups (i.e., Intervention versus Comparator) were performed using Student *t* test or Chi-square test, as appropriate. Secondly, a partially-adjusted (accounting for age, gender, GIR score and 25(OH)D concentration) and a full adjusted Cox regression were used to examine the associations of 3-month mortality (dependent variable) with vitamin D3 supplementation and covariables (independent variables). Finally, the elapsed time to death was studied by survival curves according to Kaplan-Meier method and compared by log-rank test. P-values <0.05 were considered significant. All statistics were performed using SAS® version 9.4 software (Sas Institute Inc) and R (R core Team, 2018).

2.6 Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). No participant or relatives objected to the use of anonymized clinical and biological data for research purposes. Ethics approval was obtained from the Ethics Board of the University Hospital of Angers, France (2020/100). The study protocol was also registered on ClinicalTrials.gov (NCT04560608) and declared to the French National Commission for Information Technology and civil Liberties (CNIL; ar20-0087v0) and.

3. RESULTS

Ninety-five participants (mean±SD, 88.0±5.5 years; 48.4% women) were included in this quasi-experimental study. The follow-up was complete for all participants. Sixty-six participants survived COVID-19 at 3 months while 29 died.

Table 1 indicates the participants' characteristics in the Intervention (n=67) and Comparator groups (n=28). The two groups were similar at baseline, except for the proportions of women and of history of malignancies (Table 1). The 3-month mortality was lower in the Intervention group compared to the Comparator group (respectively, 23.9% versus 46.4%, P=0.030).

Table 2 shows that, while considering the Comparator group as the reference (hazard ratio (HR)=1), the HR for mortality in the Intervention group was 0.38 [95% confidence interval (CI): 0.18;0.80] (P=0.010) in the unadjusted model, and HR=0.30 [95% CI: 0.13;0.70] (P=0.005) after partial adjustment, and HR=0.23 [95% CI: 0.09;0.58] (P=0.002) after full adjustment. Consistently, Kaplan-Meier distributions showed that COVID-19 participants in the Intervention group had longer survival time than participants in the Comparator group (log-rank P=0.008; Figure 1).

4. DISCUSSION

The present quasi-experimental study in geriatric patients with COVID-19 found that, irrespective of all measured potential confounders, vitamin D3 supplementation was associated with better survival after 3 months.

This result is consistent with observational data collected during the pandemic showing that vitamin D status is associated with COVID-19 outcomes; cases with COVID-19 and hypovitaminosis D being more likely to experience severe forms of COVID-19 (8), to require non-invasive ventilation (9), to have prolonged hospital stay (10), and to die from COVID-19 (8). Overall, these results suggest that improving vitamin D status may prevent

and/or improve severe forms of COVID-19. Consistently, preliminary results of the *Koronastudien.no* study in Norway showed that regular consumers of cod liver oil had a lower risk of COVID-19 and, in case of infection, to develop severe COVID-19 (11). Similarly, a randomized placebo-controlled clinical trial in 40 COVID-19 patients initially deficient in vitamin D showed that a greater proportion of those who received a high dose of vitamin D (i.e., 60,000 IU/day for 7 days) no longer had SARS-CoV-2 viral RNA detectable at 21 days on oropharyngeal samples compared to the placebo group (63% versus 21% respectively; P=0.018) (12). Two French quasi-experimental studies also reported that vitamin D3 supplementation was associated with better 14-day survival in older COVID-19 cases either hospitalized (3) or living in nursing-homes (6). In Spain, a pilot randomized trial found in 76 adults (mean, 53 years; 40.8% women) hospitalized for COVID-19 that calcifediol treatment (i.e., 25(OH)D) combined with standard care reduced the number of admissions to intensive care units compared to standard care alone (respectively, 2% versus 50%; P<0.001) (13), suggesting prevention of severe forms of COVID-19 by this metabolite of vitamin D. Finally, a randomized controlled trial conducted in Brazil, which randomly assigned 240 patients hospitalized for moderate- to-severe Covid-19 to 200,000 IU vitamin D3 supplementation or placebo administered 10.3 days after symptoms onset on average, did not find any effect of vitamin D supplementation on the length of hospital stay (14). The latter study was however limited by the late administration of vitamin D (10.3 days after symptoms onset on average), the relative young age of the participants (mean, 56 years), and the high proportion of patients who already had a satisfactory vitamin D status at baseline and for whom no extra benefits were expected from an extra dose of vitamin D supplements (15).

How vitamin D supplementation improves COVID-19 outcomes is not fully elucidated (16,17). First, vitamin D modulates the renin-angiotensin system, notably the angiotensin-2 converting enzyme (ACE2) (18), the expression of which is downregulated by the SARS-

CoV-2 (19) with potential consequences on inflammatory chain reaction (i.e., cytokine storm) complicated by acute respiratory distress syndrome (ARDS) (1). A study in rats with chemically-induced ARDS showed that levels of ACE2 mRNA and proteins were increased following vitamin D administration, and ARDS symptoms and lung damages were milder under vitamin D compared to controls (20). Second, vitamin D exerts antiviral effects both by induction of antimicrobial peptides with direct antiviral activity and by immunomodulatory and anti-inflammatory effects (21). These are important to limit the cytokine storm by reducing the production of pro-inflammatory cytokines by T helper 1 cells (Th1), such as Tumor Necrosis Factor-alpha (TNF-α) and interferon-γ (21), and by increasing the expression of anti-inflammatory cytokines by macrophages (21). This may explain why the prevention of mortality in the vitamin D group was most apparent in the first 14 days of the disease (Figure 1), which corresponds to the cytokine storm when inflammatory lung damage is most severe. Our study confirms the slowing of deaths beyond this period in the non-supplemented group and reports a similar evolution of the death curve in the vitamin D group, which is crucial in the perspective of increased use of vitamin D supplements during COVID-19. Third, vitamin D may have beneficial effects over time on comorbidities that are risk factors for severe forms of COVID-19, such as malignancies, diabetes mellitus, high blood pressure, chronic cardiovascular and respiratory diseases for example (5).

The low number of patients consuming daily vitamin D supplements in the present study did not allow a comparison of the effect of daily versus bolus doses on the prognosis of COVID-19. It has been previously shown in a meta-analysis, which included individual intention-to-treat data from almost 11,000 patients from 25 randomized controlled trials (22), a reduction in the risk of acute respiratory infections that was the greatest (ie, -70% [95CI%: -47;-83]) when daily or weekly doses were administered to individuals deficient in vitamin D. However, if the superiority of long-term vitamin D daily consumption is confirmed for the

prevention of infections, the reasoning cannot be the same within those already infected for the prevention of serious forms and mortality. Supplementation at small daily doses started during COVID-19 is very unlikely to correct hypovitaminosis D fast enough and exert immunomodulatory effects to improve the prognosis of the infection. In contrast, vitamin D boluses administered before or early in the disease are most likely to quickly increase the 25(OH)D concentration and to improve the prognosis of COVID-19 (if confirmed). Compared to daily doses, bolus doses have the additional merit of being preferred by patients (23) and of improving treatment adherence in older adults (24).

We also found that increased 25(OH)D concentrations at the time of COVID-19 diagnosis were associated with lower 3-month mortality (Table 2). This result is consistent with previous literature that reported higher mortality risk in COVID-19 patients exhibiting hypovitaminosis D (8), which validates the consistency of our cohort and thereby of our main finding on the benefits of vitamin D3 supplementation on the survival of older adults with COVID-19.

The strengths of the present study include i) the originality of the research question on a pandemic for which there is no scientifically validated treatment and for which the initial optimism regarding the development of COVID-19 vaccines has been tempered by the emergence of new variants of SARS-CoV-2 (1), ii) the long follow-up and the measure of longitudinal associations according to initial vitamin D intervention, and iii) the standardized collection of data from a single research center.

Several limitations also existed. First, participants were restricted to a limited number of geriatric patients who might be unrepresentative of all older adults. Second, although we were able to control for important characteristics that could modify the association, residual potential confounders might still be present, such as the 25(OH)D concentration ultimately reached following supplementation or the date of the most recent vitamin D intake. A

supplement taken in the month preceding the infection seems however to be more protective than an earlier supplementation (6). Third, the quasi-experimental design of our study is less robust than a randomized controlled trial. Participants in the Comparator group did not receive vitamin D placebo and there was no randomization. It is plausible that patients refused taking vitamin D supplementation in the Comparator group due to comorbidities such as malignancies that were too severe to take the supplements. It should yet be noted that most characteristics did not differ between the two groups, except for the history of malignancies and the proportion of women (who are likely to suffer from osteoporosis and may have received corresponding treatment that includes vitamin D).

In conclusion, we found that vitamin D3 supplementation prior to or during COVID-19 was associated with better survival after 3 months in older adults with COVID-19. Vitamin D supplementation may represent an effective, accessible, and well-tolerated adjuvant treatment for COVID-19.

Disclosures

CA occasionally serves as a consultant for Mylan Laboratories. All authors declare they do not have any other financial and personal conflicts of interest with this manuscript.

Sponsor's role

None.

CONFLICT OF INTEREST STATEMENT

CA occasionally serves as a consultant for Mylan Laboratories Inc (2020). All authors declare they do not have any other financial and personal conflicts of interest with this manuscript.

SPONSOR'S ROLE

None.

AUTHORS CONTRIBUTION

- CA has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsors. All authors have read and approved the manuscript.
- Study concept and design: CA.
- Acquisition of data: CA, MB, RS, MG, MO and JG.
- Analysis and interpretation of data: CA, TC and JG.
- Drafting of the manuscript: CA.
- Critical revision of the manuscript for important intellectual content: MB, RS, MG, MO, TC and JG.
- Obtained funding: Not applicable.
- Statistical expertise: JG.
- Administrative, technical, or material support: CA.
- Study supervision: CA.

DATA AVAILABILITY

Patient level data are freely available from the corresponding author at Cedric.Annweiler@chu-angers.fr. There is no personal identification risk within this anonymized raw data, which is available after notification and authorization of the competent authorities.

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Table 1. Characteristics and comparisons of participants with COVID-19 according to the study group (n=95)

	All COVID-19 participants (n=95)	Study group		P-value*
		Comparator group (n=28)	Vitamin D group (n=67)	
Demographical data				
Age (years), mean±SD	88.0±5.5	88.6±5.7	87.7±5.4	0.694
Female gender	46 (48.4)	8 (28.6)	38 (56.7)	**0.012**
GIR score (/6), mean±SD	3.5±1.5	3.6±1.7	3.5±1.4	0.679
Comorbidities				
Severe undernutrition†	27 (28.4)	10 (35.7)	17 (25.4)	0.308
History of malignancies	32 (33.7)	14 (50.0)	18 (26.9)	**0.030**
History of cardiomyopathy	50 (52.6)	16 (57.1)	34 (50.8)	0.569
Hospitalization				
Number of acute health issues, mean±SD	3.0±1.6	2.6±1.9	3.0±1.5	0.224
Use of antibiotics‡	64 (67.4)	19 (67.9)	45 (67.2)	0.948
Use of systemic corticosteroids	17 (17.9)	4 (14.3)	13 (19.4)	0.553
Serum 25(OH)D concentration (nmol/L), mean±SD	65.2±34.8	73.9±32.1	61.6±35.4	0.086
Follow-up				
3-month mortality	29 (30.53)	13 (46.4)	16 (23.9)	**0.030**

Data presented as n (%) where applicable; 25(OH)D: 25-hydroxyvitamin D; COVID-19: Coronavirus Disease 2019; GIR: Iso Resource Groups; *: between-group comparisons based on Chi-square test and Student *t* test, as appropriate; †: serum albumin concentration < 30 g/L; ‡: quinolones, beta-lactams, sulfonamides, macrolides, lincosamides, aminoglycosides, among others.

Table 2. Multiple Cox proportional-hazards model showing the hazard ratio for 3-month mortality among COVID-19 participants (dependent variable) according to vitamin D intervention (independent variable) adjusted for potential confounders (n=95).

	3-month mortality					
	Unadjusted model		Partially-adjusted model*		Fully-adjusted model	
	HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Vitamin D supplementation	0.38 [0.18;0.80]	**0.010**	0.30 [0.13;0.70]	**0.005**	0.23 [0.09;0.58]	**0.002**
Age	1.02 [0.95;1.09]	0.651	1.01 [0.94;1.08]	0.848	1.04 [0.95;1.13]	0.436
Female gender	0.53 [0.25;1.15]	0.109	0.82 [0.35;1.96]	0.656	0.65 [0.23;1.84]	0.417
GIR score	0.70 [0.53;0.92]	**0.010**	0.66 [0.50;0.86]	**0.003**	0.71 [0.52;0.97]	**0.029**
Serum 25(OH)D concentration	1.00 [0.99;1.01]	0.394	0.99 [0.98;1.00]	**0.049**	0.99 [0.97;1.00[	**0.035**
Severe undernutrition†	1.78 [0.84;3.78]	0.131	-	-	1.36 [0.57;3.26]	0.489
History of malignancies	3.11 [1.49;6.47]	**0.003**	-	-	2.99 [1.35;6.60]	**0.007**
History of cardiomyopathy	1.14 [0.55;2.37]	0.724	-	-	0.85 [0.37;1.97]	0.699
Number of acute health issues	1.30 [1.04;1.63]	**0.024**	-	-	1.34 [1.05;1.72]	**0.018**
Use of antibiotics‡	2.58 [0.98;6.76]	0.054	-	-	2.32 [0.78;6.94]	0.132
Use of systemic corticosteroids	0.78 [0.76;4.17]	0.184	-	-	2.39 [0.82;7.00]	0.111

25(OH)D: 25-hydroxyvitamin D; CI: confidence interval; COVID-19: coronavirus disease 2019; GIR: Iso Resource Groups; HR: hazard ratio; *: adjusted for age, sex, GIR score and 25(OH)D concentration; †: serum albumin concentration < 30 g/L; ‡: quinolones, beta-lactams, sulfonamides, macrolides, lincosamides, aminoglycosides, among others.

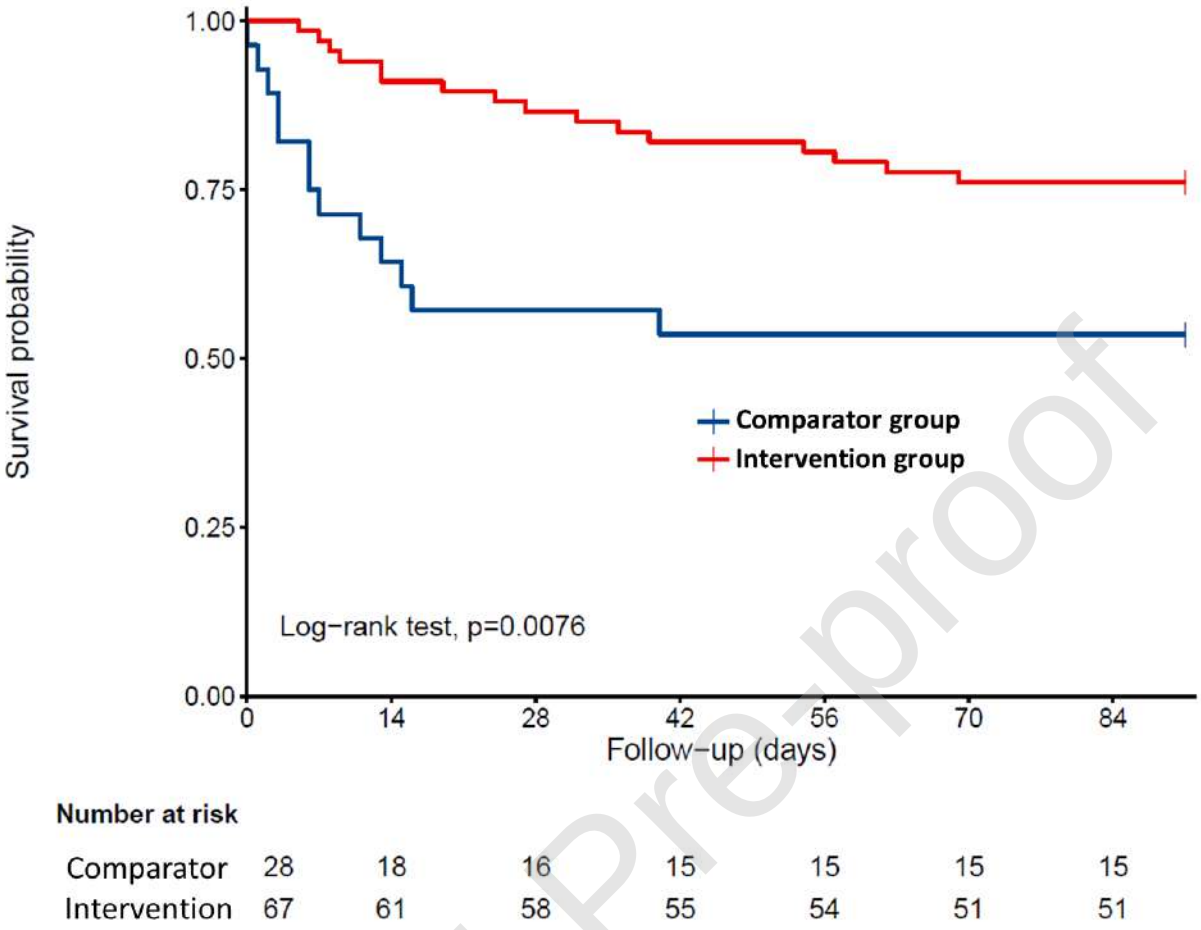

Figure 1. Kaplan-Meier estimates of the cumulative probability of COVID-19 participants' survival according to vitamin D intervention (n=95).