D.2.1.2 Annweiler 2020a

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Bibliographic Reference	Annweiler, Gaelle; Corvaisier, Mathieu; Gautier, Jennifer; Dubee, Vincent; Legrand, Erick; Sacco, Guillaume; Annweiler, Cedric; Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study.; Nutrients; 2020; vol. 12 (no. 11)

Study details

Trial registration number and/or trial name	Not reported.
Study type	Retrospective cohort study
Study location	France
Study setting	Hospital, Angers University Hospital.
Study dates	March-May 2020
Sources of funding	Funding reported as "not applicable".
Inclusion criteria	Patients hospitalized in the geriatric acute care unit of the hospital No objection from the patient and/or relatives to the use of anonymized clinical and biological data for research purpose

	COVID-19 diagnosed with RT-PCR and/or chest CT-scan Data available on the treatments received, including vitamin D supplementation, since the diagnosis of COVID-19 and over the preceding year at least Data available on the vital status 14 days after the diagnosis of COVID-19
Exclusion criteria	Not reported
Intervention(s)	The regular intake of bolus vitamin D supplements over the preceding year was systematically noted from the primary care physicians' prescriptions and sought by questioning the patients and their relatives. "Group 1" was defined as all COVID-19 patients who had received oral boluses of vitamin D supplements over the preceding year. Bolus included the doses of 50,000 IU vitamin D_3 per month, or the doses of 80,000 IU or 100,000 IU vitamin D_3 every 2–3 months. None received D_2 or intramuscular supplements, and no patient in Group 1 received additional supplements following the diagnosis of COVID-19. "Group 2" was defined as the COVID-19 patients usually not supplemented with vitamin D, but who received an oral supplement of 80,000 IU vitamin D_3 within a few hours of the diagnosis of COVID-19.
Comparator	"Group 3" was all COVID-19 patients who had received no vitamin D supplements, neither over the preceding year nor after the diagnosis of COVID-19. The absence of vitamin D treatment being mostly explained by the patients' refusal to be supplemented, since vitamin D supplementation is recommended with no biological testing in all patients over 65 years of age in France.
Outcome measures	COVID-19 mortality Within 14 days of COVID-19 diagnosis. Follow-up continued for 14 days or until death. OSCI score for COVID-19 in acute phase The score on the 9-pointWorld Health Organization's ordinal scale for clinical improvement (OSCI) for COVID-19. The OSCI distinguishes between several levels of COVID-19 clinical severity according to the outcomes and dedicated treatments required, with a score ranging from 0 (no clinical or virological sign of infection) to 8 (death). The score was determined by the geriatrician of the hospital unit on admission, then revised regularly according to the clinical course of the patients. The highest score during hospitalization was used for the present analysis, corresponding to the most severe acute phase of COVID-19 for each patient. A score of 3 corresponds to a degree of severity requiring hospitalization (i.e., all GERIA-COVID participants had an OSCI score ≥3 here), a score of 5 corresponds to the introduction of non-invasive ventilation, and a score of 6 to intubation and invasive ventilation. Severe COVID-19 was defined here as a score of 5 or more.
Number of participants	N=77 Group 1, n=29

	Group 2, n=16 Group 3, n=32
Duration of follow-up	14 days or until death.
Loss to follow-up	None reported.
Methods of analysis	The participants' characteristics were summarized using means and standard deviations (SD) or frequencies and percentages, as appropriate. As the number of observations was higher than 40, comparisons were not affected by the shape of the error distribution and no transformation was applied. 4 models were made: 1) comparisons between groups for the reported outcomes; 2) the association between each group and 14-day mortality at a specific time, adjusting for confounders; 3) comparison of survival between the groups; 4) association between vitamin D status and severe COVID-19, adjusted for confounding variables. 1) Comparisons between participants separated into three groups according to the intervention (i.e., regular supplementation versus supplementation initiated after COVID-19 diagnosis versus no supplementation) were performed using analysis of variance (ANOVA) or Mann–Whitney–U and Kruskal–Wallis tests for quantitative variables as appropriate, and using Chi-square test or Fisher exact test for qualitative variables as appropriate. To address the issue of multiple comparisons, analyses were completed by a post hoc Fisher's least significant difference (LSD) test. 2) A fully adjusted Cox regression was used to examine the associations of 14-day mortality (dependent variable) with vitamin D supplementation and covariables (independent variables). The model produces a survival function that provides the probability of death at a given time for the characteristics supplied for the independent variables. 3) The elapsed time to death was studied by survival curves computed according to the Kaplan–Meier method and compared by log-rank test. 4) A multiple logistic regression was used to examine the association of vitamin D supplementation (independent variable) with severe COVID-19 defined as an OSCI score ≥5 (dependent variable), while adjusting for potential confounders. p-values <0.05 were considered significant. All statistics were performed using SPSS and SAS.
Study limitations (authors)	The study participants were restricted to a limited number of hospitalized frail elderly patients who might be unrepresentative of all older adults. It is also possible that the limited sample size in each group had resulted in a lack of power with increased beta risk.

	The study aimed to control for the important characteristics that could modify the association, but residual potential confounders might still be present such as the serum concentration of 25(OH)D at baseline, a low level classically ensuring the efficacy of the supplementation, or the OSCI score on admission. The OSCI score was collected in the most acute phase of COVID-19 as it was reported that COVID-19 can get worse between 7–10 days due to the cytokine storm regardless of the initial disease severity. The quasi-experimental design is less robust than an RCT. Participants in the comparator group did not receive vitamin D placebo. Moreover, there was no randomization. It is plausible that the participants who regularly received vitamin D supplementation (Group 1) were treated better by their family physicians than the others, thereby exhibiting more stable chronic diseases such as cardiovascular comorbidities. It is also plausible that patients or relatives refused taking vitamin D supplementation in Group 3, because the conditions of patients were too severe for them to take the supplements. The authors noted that the history did not differ between the 3 groups and that their demographical and health characteristics were similar at baseline. However, the proportion of women who are likely to suffer from osteoporosis and may have received corresponding treatment that includes vitamin D.
Study limitations (reviewer)	Estimations of vitamin D status based on supplementation may be incorrect as it relies on medicine compliance.

Study arms

Regular vitamin D supplementation (N = 29)
Vitamin D supplementation after COVID-19 (N = 16)
Non-supplemented comparator (N = 32)

Characteristics

Study-level characteristics

	Study (N = 77)
Ethnicity	
Custom value	NA

	Study (N = 77)
BMI	
Custom value	NA
Use of immune suppressing treatments	
Custom value	NA
Socioeconomic status	
Custom value	NA
Previous history of COVID-19	
Custom value	NA
Other supplement use	
Custom value	NA
Timing of vitamin D measurements	
Custom value	NA
Shielding status	
Custom value	NA
Living in care homes	
Custom value	NA
Vitamin D status	

	Study (N = 77)
Custom value	NA

Arm-level characteristics

	Regular vitamin D supplementation (N = 29)	Vitamin D supplementation after COVID-19 (N = 16)	Non-supplemented comparator (N = 32)
Age			
MedianIQR	88 (87 to 93)	85 (84 to 89)	88 (84 to 92)
% Female			
Sample Size	n = 20 ; % = 69	n = 5 ; % = 31.3	n = 13 ; % = 40.6
Comorbidities			
Severe undernutrition Serum albumin concentration <30 g/L			
Sample Size	n = 9 ; % = 31	n = 3 ; % = 18.8	n = 9 ; % = 28.1
Haematological and solid cancers			
Sample Size	n = 10 ; % = 34.5	n = 4 ; % = 25	n = 13 ; % = 40.6
Hypertension			
Sample Size	n = 18 ; % = 62.1	n = 10 ; % = 62.5	n = 21 ; % = 65.6
Cardiomyopathy			
Sample Size	n = 13 ; % = 44.8	n = 11 ; % = 68.8	n = 18 ; % = 56.3

	Regular vitamin D supplementation (N = 29)	Vitamin D supplementation after COVID-19 (N = 16)	Non-supplemented comparator (N = 32)
Number of acute health issues at hospital admission			
MedianIQR	3 (2 to 4)	3.5 (2 to 5)	2.5 (1 to 4)
CRP at admission *(mg/L)*			
MedianIQR	44 (19 to 110)	69 (15.5 to 140)	59 (29 to 166)
Use of antibiotics			
Sample Size	n = 23 ; % = 79.3	n = 14 ; % = 87.5	n = 22 ; % = 68.8
Use of systemic corticosteroids			
Sample Size	n = 6 ; % = 20.7	n = 2 ; % = 12.5	n = 5 ; % = 15.6
Use of pharmacological treatments of respiratory disorders			
Sample Size	n = 1 ; % = 3.5	n = 2 ; % = 12.5	n = 7 ; % = 21.9
Glycated haemoglobin *(%)*			
MedianIQR	6 (5.5 to 6.6)	6.4 (6 to 8.2)	6.2 (5.9 to 6.7)

Outcomes

COVID-19 outcomes

	Regular vitamin D supplementation	Vitamin D supplementation after COVID-19	Non-supplemented comparator
	N = 29	N = 16	N = 32
Severe COVID-19 defined as an OSCI score for COVID-19 in acute phase ≥5 *Polarity: Lower values are better*			
Sample Size	n = 3 ; % = 10.3	n = 4 ; % = 25	n = 10 ; % = 31.3
14-day mortality *Polarity: Lower values are better*			
Sample Size	n = 2 ; % = 6.9	n = 3 ; % = 18.8	n = 10 ; % = 31.3

Association between vitamin D supplementation and COVID-19 outcomes

Results from the Cox regression. Adjusted for age, gender, GIR score, severe undernutrition, history of cancer, history of hypertension, history of cardiomyopathy, glycated haemoglobin, number of acute health problems, use of antibiotics, use of systemic corticosteroids, use of treatments of respiratory disorders.

	Regular vitamin D supplementation vs Non-supplemented comparator	Vitamin D supplementation after COVID-19 vs Non-supplemented comparator
	N1 = 29, N2 = 32	N1 = 16, N2 = 32
Mortality Evaluated by Cox regression *Polarity: Lower values are better*		
Hazard ratio/95% CI	0.07 (0.01 to 0.61)	0.37 (0.06 to 2.21)

	Regular vitamin D supplementation vs Non-supplemented comparator	Vitamin D supplementation after COVID-19 vs Non-supplemented comparator
	N1 = 29, N2 = 32	N1 = 16, N2 = 32
Severe COVID-19 Evaluated by multiple logistic regression *Polarity: Lower values are better*		
Odds ratio/95% CI	0.08 (0.01 to 0.81)	0.46 (0.07 to 2.85)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias (*Important baseline characteristics, such as BMI, ethnicity, use of other supplements and socioeconomic status not included)*
Study Attrition	Study Attrition Summary	Low risk of bias (*no attrition reported*)
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias (*Method for ensuring prognostic factor was received appropriately for each group not reliable – vitamin D supplements assumed to be taken at home and adherence cannot be guaranteed)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias (*outcomes were objective and/or a valid, recognised tool for measuring COVID-19 severity, completed by geriatrician but 14 days was short for follow-up)*
Study Confounding	Study Confounding Summary	High risk of bias (*Important confounders, such as BMI, ethnicity, use of other supplements and socioeconomic status not included)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias (*Many factors adjusted for in small cohort likely to lead to overfitting; Important confounders, such as BMI, ethnicity, use of other supplements and socioeconomic status not accounted for in analyses)*
Overall risk of bias and directness	Risk of Bias	High
	Directness	Directly applicable