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Bibliographic Reference	Radujkovic, Aleksandar; Hippchen, Theresa; Tiwari-Heckler, Shilpa; Dreher, Saida; Boxberger, Monica; Merle, Uta; Vitamin D Deficiency and Outcome of COVID-19 Patients.; Nutrients; 2020; vol. 12 (no. 9)

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not reported.
Study start date	18-Mar-2020
Study end date	18-Jun-2020
Aim of the study	To explore possible associations between vitamin D status and disease severity and survival in COVID-19 patients.
County/ Geographical location	Heidelberg, Germany
Study setting	Hospital

Population description	Consecutive symptomatic SARS-CoV2-positive patients admitted to the Medical University Hospital Heidelberg enrolled onto a prospective non-interventional register.
Inclusion criteria	Participant consent and serum samples available for analysis.
Exclusion criteria	None reported.
Vitamin D status measurements	To assess whole-body vitamin D status of patients, levels of total 25(OH)D were measured retrospectively in cryopreserved (-80°C) serum samples collected in gel tubes at the time of admission and SARS-CoV-2 testing. Serum levels of total 25(OH)D were quantified using a commercially available immunoassay (ADVIA Centaur Vitamin D Total Assay®, Siemens Healthcare GmbH, Erlangen, Germany). All measurements were carried out at the Department of Clinical Chemistry of the Heidelberg University Hospital using accredited laboratory methods (certified according to ISO 15189 by Germany's national accreditation body).
Methods used to confirm COVID-19 infection	RNA from nasopharyngeal and oropharyngeal swabs was analysed using QIAGEN kits on QIASymphony or QIAcube devices. Varies RT-PCR reagent mixes were used: LightMix Modular SARS and Wuhan CoV E-gene, LightMix Modular SARS and Wuhan CoV N-gene, LightMix ModularWuhan CoV RdRP-gene, and LightMix Modular AV RNA Extraction Control (as internal control) from TIB MOLBIOL Syntheselabor GmbH (Berlin, Germany), and LightCycler Multiplex RNA Virus Master (Roche, Mannheim, Germany). The decision for inpatient versus outpatient admission was based on the level of spontaneous oxygen saturation (SpO2 ≤ 93%), comorbidities, and the overall performance status. With regard to established COVID-19 severity classifications, all inpatients had severe disease (defined as tachypnoea [≥30 breaths per min], oxygen saturation ≤ 93% at rest, or PaO2/FiO2 ratio < 300 mm Hg) or critical disease (respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care). Outpatients included in the analysis had symptomatic disease presenting with fever, cough, sore throat, myalgia, and/or fatigue. Outpatients were visited in their home quarantine on a regular basis and their clinical conditions were regularly evaluated employing "Coronataxis" (i.e., home visits by medical students, nursing staff, and a supervising physician) which were implemented by the University Hospital Heidelberg and the regional health authorities.
Intervention	Not applicable
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	Described elsewhere

Methods for case-matching with control	Not applicable
Methods of data analysis	Categorical data of patient characteristics were compared using Fisher's exact test. Continuous Median follow-up time was calculated by the reverse Kaplan-Meier method. Two endpoints were reported: severe course of disease (need for invasive mechanical ventilation and/or death, IMV/D, as a composite endpoint) and death of any cause. Survival was calculated from the date of first presentation/admission and SARS-CoV-2 testing to last follow-up or death of any cause. Patients alive were censored at the date of last contact. Severe course of the disease was determined as time from the date of first presentation/admission and SARS-CoV-2 testing to IMV/D. Patients who were alive without necessary IMV were censored at the time of the last contact. Vitamin D deficiency was defined as serum total 25(OH)D level < 12 ng/mL (equivalent to <30 nM). In addition, the cut-point of 25(OH)D < 20 ng/mL (<50 nM) reflecting “Vitamin D insufficiency” was analysed. For uni- and multivariable analysis of the associations between Vitamin D status and severe course of the disease and survival, Cox regression models were applied. For the multivariable analyses, additional prognostic factors including age, gender, and presence of comorbidity were chosen to reflect confounders demonstrated to be associated with risk of death. All statistical tests were two-sided at a significance level of 5%. Hazard ratios (HR) were estimated with 95% confidence interval (95% CI). Calculations were done using IBM® SPSS® Statistics, Version 24.0.0.
Source of funding	No external funding declared.
Other details	Oxygen therapy included oxygen delivery via nasal cannula, high-low nasal oxygen therapy (HFNO), and invasive mechanical ventilation (IMV). Criteria for initiation of IMV were failure to maintain adequate ventilation or oxygenation in spite of high FiO2 delivery. Hospitalized patients were treated with standard supportive care including antibiotic and antifungal therapy, whereas additional immunomodulatory therapy was inconsistently applied (azithromycin, hydroxychloroquine, tocilizumab, anakinra, prednisolone, maraviroc, Cytosorb, and plasmapheresis). Routine CT scans were performed at hospital admission for most patients.
Study limitations (authors)	A single-centre, retrospective, and observational study. In particular, since the number of events is rather low, the results require confirmation in larger patient cohorts analysing a higher number of events and considering additional potential confounders like obesity (as reflected by the body mass index) or other specific comorbidities. It should be noted that without randomized controlled trial evidence, no causal association between Vitamin D deficiency and severity/outcome of COVID-19 can be inferred. However, since no causal treatment for COVID-19 is available, identification of modifiable prognostic factors may help to improve outcomes.

Study limitations (reviewer)	Such a large number of adjustments for low event rates lends itself to overfitting, limiting generalisability outside of this cohort. It also can cause imprecise effect estimates and large effects can arise from small changes in the raw data. Therefore the uncertainty in these effect estimates is very high and likely to change with further publication of evidence. There could be differences in the clinical decisions made before ventilation due to this study not being in the UK and changes over the course of the pandemic.

Study arms

Vitamin D <12 ng/mL (N = 41) Participants with serum vitamin D less than 12 ng/mL
Vitamin D ≥12 ng/mL (N = 144) Participants with serum vitamin D greater than or equal to 12 ng/mL

Characteristics

Arm-level characteristics

	Vitamin D <12 ng/mL (N = 41)	Vitamin D ≥12 ng/mL (N = 144)
Age		
MedianIQR	66 (53 to 78)	58 (47 to 67)
Inpatients n=93		
MedianIQR	71 (54 to 79)	62 (50 to 70)
Outpatients n=92		
MedianIQR	60 (48 to 77)	55 (42 to 63)
Gender Male		
Sample Size	n = 23 ; % = 56	n = 72 ; % = 50
Inpatients		

	Vitamin D <12 ng/mL (N = 41)	Vitamin D ≥12 ng/mL (N = 144)
n=93		
Sample Size	n = 19 ; % = 66	n = 40 ; % = 62
Outpatients n=92		
Sample Size	n = 4 ; % = 33	n = 32 ; % = 40
Ethnicity		
Custom value	NA	NA
Comorbidities Any		
Sample Size	n = 22 ; % = 54	n = 55 ; % = 38
Inpatients n=93		
Sample Size	n = 19 ; % = 66	n = 33 ; % = 52
Outpatients n=92		
Sample Size	n = 3 ; % = 25	n = 22 ; % = 27
BMI		
Custom value	NA	NA
Use of immune suppressing treatments		
Custom value	NA	NA
Socioeconomic status		
Custom value	NA	NA
Previous history of COVID-19		
Custom value	NA	NA
Other supplement use Vitamin D		
Sample Size	n = 0 ; % = 0	n = 6 ; % = 7
Inpatients n=93		
Sample Size	n = 0 ; % = 0	n = 6 ; % = 9

	Vitamin D <12 ng/mL (N = 41)	Vitamin D ≥12 ng/mL (N = 144)
Outpatients n=92		
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0
Timing of vitamin D measurements		
Custom value	NA	NA
Shielding status		
Custom value	NA	NA
Living in care homes		
Custom value	NA	NA
Cardiovascular disease		
Sample Size	n = 18 ; % = 44	n = 40 ; % = 28
Inpatients n=93		
Sample Size	n = 17 ; % = 59	n = 28 ; % = 44
Outpatients n=92		
Sample Size	n = 1 ; % = 8	n = 12 ; % = 15
Diabetes		
Sample Size	n = 8 ; % = 20	n = 11 ; % = 8
Inpatients n=93		
Sample Size	n = 6 ; % = 21	n = 7 ; % = 11
Outpatients n=92		
Sample Size	n = 2 ; % = 17	n = 4 ; % = 5
Chronic kidney disease		
Sample Size	n = 2 ; % = 5	n = 6 ; % = 4
Inpatients n=93		
Sample Size	n = 2 ; % = 7	n = 6 ; % = 9

	Vitamin D <12 ng/mL (N = 41)	Vitamin D ≥12 ng/mL (N = 144)
Outpatients n=92		
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0
Chronic lung disease		
Sample Size	n = 6 ; % = 15	n = 9 ; % = 6
Inpatients n=93		
Sample Size	n = 6 ; % = 21	n = 4 ; % = 6
Outpatients n=92		
Sample Size	n = 0 ; % = 0	n = 5 ; % = 6
History of malignancy		
Sample Size	n = 5 ; % = 12	n = 12 ; % = 8
Inpatients n=93		
Sample Size	n = 4 ; % = 14	n = 5 ; % = 8
Outpatients n =92		
Sample Size	n = 1 ; % = 8	n = 7 ; % = 9
Maximum oxygen therapy		
Sample Size	n = 26 ; % = 54	n = 54 ; % = 38
Inpatients n=93		
Sample Size	n = 26 ; % = 90	n = 54 ; % = 86
Outpatients n=92		
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0

Outcomes

Associations of Vitamin D Status with the Endpoints Invasive Mechanical Ventilation and/or Death and Death

Results from Cox regression analysis and reverse Kaplan Meier survival analysis. Composite endpoint includes mechanical ventilation and death to produce hazard ratios of cumulative incidence. Survival analysis assesses death only. Adjusted values take into account age, gender, and comorbidities.

	Vitamin D <12 ng/mL vs Vitamin D ≥12 ng/mL
	N1 = 41, N2 = 144
Cumulative incidence, whole cohort *Polarity: Lower values are better*	
Unadjusted	
Hazard ratio/95% CI	7.66 (3.53 to 16.63)
Adjusted	
Hazard ratio/95% CI	6.12 (2.79 to 13.42)
Cumulative incidence, inpatients only *Polarity: Lower values are better*	
Unadjusted	
Hazard ratio/95% CI	5.24 (2.41 to 11.42)
Adjusted	
Hazard ratio/95% CI	4.65 (2.11 to 10.25)
Death, whole cohort *Polarity: Lower values are better*	
Unadjusted	
Hazard ratio/95% CI	18.05 (5.14 to 63.43)
Adjusted	
Hazard ratio/95% CI	14.73 (4.16 to 52.19)
Death, inpatients only *Polarity: Lower values are better*	
Unadjusted	
Hazard ratio/95% CI	12.31 (3.5 to 43.34)
Adjusted	
Hazard ratio/95% CI	11.51 (3.24 to 40.92)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Ethnicity not included.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(No attrition reported.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Immunoassay conducted for all participants.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Standardised outcome measurements, events hard to misclassify.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Ethnicity and immunosuppressant use missing.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Possible confounding caused by not controlling for ethnicity and immunosuppressants.)*
	Directness	Directly applicable *(There could be differences in the clinical decisions made before ventilation due to this study not being in the UK and changes over the course of the pandemic)*