D.2.1.12 Ye 2020

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Bibliographic Reference	Ye, Kun; Tang, Fen; Liao, Xin; Shaw, Benjamin A; Deng, Meiqiu; Huang, Guangyi; Qin, Zhiqiang; Peng, Xiaomei; Xiao, Hewei; Chen, Chunxia; Liu, Xiaochun; Ning, Leping; Wang, Bangqin; Tang, Ningning; Li, Min; Xu, Fan; Lin, Shao; Yang, Jianrong; Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity?-A Case-Control Study.; Journal of the American College of Nutrition; 2020; 1-8

Study details

Study design	Case–control study
Trial registration (if reported)	Not reported.
Aim of the study	To assess the association between 25(OH)D levels and COVID-19 disease, its severity, and its clinical characteristics in a Chinese population.
County/ Geographical location	Nanning, China.
Study setting	Hospital
Population description	The cases included all patients with COVID-19 disease, from February 16th, 2020 to March 16th, 2020, treated at the Yongwu Hospital of The People's Hospital of Guangxi Zhuang Autonomous Region (n=62). Controls were recruited from The Physical Examination Center at the Institution with no medical disorder (hypertension, diabetes, renal disease, and pneumonia), and were frequency matched by sex and age as the cases (n=80). The study also compared participants with different severity of COVID-19. The participants in the mild/moderate (n=50) and severe/critical (n=10) arms are from the COVID-19 positive cohort. 2 participants from the positive cohort were asymptomatic and do not appear in either mild/moderate or severe/critical arms.
Inclusion criteria	Cases had to be positive according to the COVID-19 test conducted.
Exclusion criteria	None reported.

Vitamin D status measurements	Serum samples were collected for each patient at admission and stored at -80 degrees C before measuring the concentration of 25-hydroxyvitamin D (25(OH)D) using an electrochemiluminescent immunoassay (ECLIA) with a Roche Elecsys 10100/201 system. The study followed the Endocrine Society clinical practice guideline, vitamin D deficiency (VDD) was defined as a 25(OH)D<50 nmol/L, vitamin D insufficiency as 50 nmol/L≤25(OH)D<75 nmol/L and vitamin D sufficiency as 25(OH)D≥75 nmol/L.
Methods used to confirm COVID-19 infection	The cases of COVID-19 were diagnosed according to the guidelines of the National Health Commission of China and were confirmed by positive SARS-CoV-2 RNA with throat swab samples (Sansure Biotechnology, Changsha, Hunan, China). Severe COVID-19 case was defined according to the guidelines of the National Health Commission of China. Severe cases met at least one of the following criteria: 1) breathing rate >30/min 2) pulse oximeter oxygen saturation (SpO2) ≤93% when breathing ambient air 3) ratio of partial oxygen pressure (PaO2) to the fraction of inspired oxygen (FiO2) ≤300mmHg (1mmHg = 0.133 kpa) 4) lung imaging showing significant progression of >50% with 24 to 48 hours Critical cases met at least 1 of the following criteria: 1) respiratory failure (PaO2 <60mmHg when breathing ambient air) 2) hemodynamic shock (persisting hypotension requiring vasopressors to maintain MAP ≥65mmHg and serum lactate level >2 mmol/L despite volume resuscitation 3) organ failure or admittance to intensive care unit (ICU). All other cases were classed as mild/moderate.
Intervention	Not applicable
Comparator (where applicable)	Not applicable

Methods for population selection/allocation	Not applicable
Methods for case-matching with control	Frequency matched controls to cases by sex and age.
Methods of data analysis	Potential confounding variables include age, sex, and comorbidities (those listed in the characteristics table) which are suspected risk factors of COVID-19 or thought to be associated with both COVID-19 infection and vitamin D deficiency. Continuous variables were presented as mean (SD) and compared with students t test, if normally distributed, or median [IQR] and Mann-Whitney U test if non-normally distributed. Categorical variables were presented as number and percentage and analysed by chi-square test or Fisher's exact test when counts were expected to be <1. 2 model were reported: an association between all measured risk factors and severe/critical disease; 2) an association between all measured risk factors and cases vs controls. These were conducted by unconditional logistic regression. SPSS 22.0 was used to conduct the analyses.
Attrition/loss to follow-up	Not loss to follow-up reported.
Source of funding	The study was supported by the Guangxi Critical Infectious Disease Center (2020281) and Nanning Science and Technology Foundation (2018030).
Study limitations (Author)	Controls were not tested for COVID-19, creating bias towards the null as infected people can be asymptomatic. Small sample size means study power was calculated to be 76.4%, lower than the standard 80% considered acceptable in epidemiological studies. This means the study may not have adequate power to accurately detect differences in clinical indicators between cases. The protective effect of serum 25(OH)D>75nmol/l is quite possibly greater than observed here which could have been better demonstrated if a wider range of serum 25(OH)D was present in the controls. The hospital is situated in a city, which takes local cases. The majority of participants were from urban areas and therefore may not be generalisable to other populations in China.

	Cases' vitamin D levels were taken during hospital admission after the onset of COVID-19. They defended this by saying that prior research has shown vitamin D level is stable and not affected by acute respiratory infection making it a good representation of vitamin D level prior to infection and admission.
Study limitations (reviewer)	There could be differences in the clinical decisions made before ICU admission due to this study not being in the UK and changes over the course of the pandemic.

Study arms

Controls (N = 80)
SARS-CoV2 positive (N = 62)
Mild/moderate COVID-19 (N = 50) Participants from the COVID-19 positive arm who had either mild or moderate symptoms
Severe/critical (N = 10) Participants from the COVID-19 positive arm who had either severe or critical symptoms

Characteristics

Arm-level characteristics

	Controls (N = 80)	COVID-19 positive (N = 62)	Mild/moderate COVID-19 (N = 50)	Severe/critical (N = 10)
Age				
MedianIQR	42 (31 to 52)	43 (32 to 59)	39 (30 to 49)	65 (54 to 69)
Gender Female				
Sample Size	n = 48 ; % = 60	n = 39 ; % = 63	n = 31 ; % = 62	n = 6 ; % = 60
Ethnicity				
Custom value	NA	NA	NA	NA
BMI				
Custom value	NA	NA	NA	NA

	Controls (N = 80)	COVID-19 positive (N = 62)	Mild/moderate COVID-19 (N = 50)	Severe/critical (N = 10)
Use of immune suppressing treatments				
Custom value	NA	NA	NA	NA
Socioeconomic status				
Custom value	NA	NA	NA	NA
Previous history of COVID-19				
Custom value	NA	NA	NA	NA
Other supplement use				
Custom value	NA	NA	NA	NA
Timing of vitamin D measurements				
Custom value	NA	NA	NA	NA
Shielding status				
Custom value	NA	NA	NA	NA
Living in care homes				
Custom value	NA	NA	NA	NA
Vitamin D status				
Deficiency				
Sample Size	n = 15 ; % = 19	n = 26 ; % = 42	n = 18 ; % = 36	n = 8 ; % = 80
Non-deficiency				
Sample Size	n = 65 ; % = 81	n = 36 ; % = 58	n = 32 ; % = 64	n = 2 ; % = 20
Comorbidities				
Diabetes				
Sample Size	n = NA	n = NA	n = 3 ; % = 6	n = 2 ; % = 20
Hypertension				
Sample Size	n = NA	n = NA	n = 4 ; % = 8	n = 2 ; % = 20
Liver injury				
Sample Size	n = NA	n = NA	n = 0 ; % = 0	n = 1 ; % = 10
COPD				

	Controls (N = 80)	COVID-19 positive (N = 62)	Mild/moderate COVID-19 (N = 50)	Severe/critical (N = 10)
Sample Size	n = NA	n = NA	n = 1 ; % = 2	n = 0 ; % = 0
Asthma				
Sample Size	n = NA	n = NA	n = 0 ; % = 0	n = 0 ; % = 0
Renal failure Defined as GRF <90mL/min*1.73m2				
Sample Size	n = NA	n = NA	n = 8 ; % = 16	n = 8 ; % = 80

Outcomes

Distribution of vitamin D level among different severity status

Participants are distributed into vitamin D sufficient, insufficient and deficient. Data are presented as sample size and percentage. Percentages represent of total number of events across whole case cohort (n=62) and not within each vitamin D status group.

	Sufficient	Insufficient	Deficient	P value
	N = 10	N = 26	N = 26	
Clinical classification of severity *Polarity: Not set*				
Asymptomatic				
Sample Size	n = 2 ; % = 100	n = 0	n = 0 ; % = 0	0.004
Mild/moderate				
Sample Size	n = 7 ; % = 14	n = 25 ; % = 50	n = 18 ; % = 36	
Severe/critical				
Sample Size	n = 1 ; % = 10	n = 1 ; % = 10	n = 8 ; % = 80	
Adverse events *Polarity: Not set*				
Shock				
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0	n = 4 ; % = 100	0.025
Mechanical ventilation				
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0	n = 5 ; % = 100	0.012

	Sufficient	Insufficient	Deficient	P value
	N = 10	N = 26	N = 26	
FiO2<300mmHg				
Sample Size	n = 1 ; % = 12.5	n = 1 ; % = 12.5	n = 3 ; % = 75	0.58
Lung infiltration				
Sample Size	n = 0 ; % = 0	n = 1 ; % = 20	n = 4 ; % = 80	0.099

Multivariable logistic regression analysis of all potential risk factors as predictors of severe/critical COVID-19.

	Severe/critical vs Mild/moderate COVID-19
	N1 = 10, N2 = 50
Vitamin deficiency *Polarity: Lower values are better*	
Odds ratio/95% CI	15.18 (1.23 to 187.45)
Age Every ten years per level (level 1-9) *Polarity: Lower values are better*	
Odds ratio/95% CI	2.45 (0.83 to 7.23)
Gender Female *Polarity: Lower values are better*	
Odds ratio/95% CI	4.21 (0.28 to 64.35)
Renal failure *Polarity: Lower values are better*	
Odds ratio/95% CI	14.14 (0.79 to 253.9)
Hypertension *Polarity: Lower values are better*	
Odds ratio/95% CI	0.52 (0.02 to 12.29)
Diabetes *Polarity: Lower values are better*	
Odds ratio/95% CI	0.58 (0.02 to 18.17)

Odds of vitamin D deficiency

Likelihood of being vitamin D deficient according to disease state. Includes comparisons between all cases vs healthy controls and mild/moderate vs severe/critical cases. Values are unadjusted comparisons.

	COVID-19 positive vs Controls	Severe/critical vs Mild/moderate COVID-19
	N1 = 62, N2 = 80	N1 = 10, N2 = 50
Vitamin D deficiency *Polarity: Lower values are better*		
Odds ratio/95% CI	3.13 (1.47 to 6.66)	7.11 (1.36 to 37.16)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(No description of BMI or ethnicity. Large number of urban participants.)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Missing BMI and ethnicity.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High *(Missing BMI and ethnicity from adjusting and baseline characteristics.)*
	Directness	Directly applicable *(There could be differences in the clinical decisions made before hospitalisation and ICU admission due to this study not being in the UK and changes over the course of the pandemic)*