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Vitamin D as a laboratory predictor of mortality in COVID-19 patients admitted in intensive care

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Abstract:

Background: Multiple blood markers were correlated with poor clinical results in severely ill COVID-19 patients. Published reports correlated C-Reactive Protein (CRP), Neutrophil-to-Lymphocyte Ratio (NLR), D-dimer, serum ferritin, and vitamin D levels, with adverse outcomes and an enhanced mortality rate in vitally ill COVID-19 patients; yet, evidence is not enough to guide management for the patients using the predictive values of the above mentioned markers. **Objectives**: to assess the impact of vitamin D on the outcomes of COVID-19 patients who were extremely ill. **Methods**: We conducted prospective research on 40 COVID-19 patients who were critically sick and hospitalized to the intensive care unit (ICU) of a chest isolation hospital in Beni Suef, Egypt (COVID intensity score ≥ 8). Vitamin D concentrations in blood were determined at admission and 48 hours later. **Results**: There were 40 patients total, with an average age of 55.6 ±9.9 years and a non-statistical significance between both sexes. With a median duration of 15 days, mechanical breathing was necessary for 62.5% of the patients (invasive and non-invasive). There was a clinical correlation between death and male sex, the existence of diabetes mellitus, bilateral pulmonary infiltration, and heart failure, despite these correlations being statistically insignificant. After admission, serum vitamin D levels did not significantly influence mortality prediction; however, 48 hours later, vitamin D significantly affected mortality prediction, with Area under curve (0,886) and sensitivity (81,8), specificity (83,3), PPV (85,7), and NPV (78,9) at a cut-off ≤ 18. **Conclusions**: vitamin D useful as a predictor for mortality. Many demographic and clinical factors must be correlated with , when interpretating this biomarker .

Keywords: COVID-19, Length of stay, Mechanical ventilation, Mortality, ICU

1. Introduction:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was the cause of Coronavirus Disease (COVID-19) in 2019. Once COVID-19 first appeared in Wuhan (China), on March 11, 2020, the World Health Organization (WHO) declared a global pandemic. [1,2].

For numerous months now, COVID-19 has posed serious health hazards to people all over the world due to the strain it has placed on healthcare systems everywhere. Patients with severe COVID-19 symptoms have blood levels of CRP that are markedly elevated, as well as many pro-inflammatory cytokines and chemokines, such as interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). [3-5].

These cytokines induce a systemically inflammation reaction that increases CD8+ cytotoxic T-cell function while concurrently lowering regulatory T-cell function when they are generated in sufficient numbers. [6].

Patients may get acute respiratory distress disorder and multiorgan dysfunction as a result of these aberrant immune responses [7,8].

The level of lymphopenia was correlated with the degree of the illness in severely sick COVID-19 patients, with a rise in neutrophil counts and a significant decrease in numbers of peripheral lymphocytes (mostly CD4+ and CD8+ T cells) "enhanced NLR". [9].

In acute COVID-19 instances, irregular coagulation results are also seen. They include markedly increased levels of fibrinogen, D- dimer, and other fibrin breakdown products, as well as Prothrombin duration was significantly prolonged, and partial thromboplastin duration was stimulated. [9,10].

These results imply that overt disseminated intravascular coagulation (DIC) may develop in the future [10].

Research has shown that vitamin D, notwithstanding its well-known function in regulating calcium and bone maintenance, also possesses anti-

inflammatory and immunomodulatory properties. [11].

According to investigations, vitamin D is essential for the regulation of both intrinsic and adapted immune responses, promoting tolerogenic responses, inhibiting the generation of a number of pro-inflammatory mediators, and enhancing antivirus action pathways. [12-15].

Vitamin D insufficiency is a global epidemic that affects greater than 1 billion persons of all ages. [16].

Moreover, variables associated with vitamin D insufficiency, like as obesity, advanced age, and Asian or Black ethnicity, are linked to those with severe COVID-19. [17].

Several investigations have noted that a lack of vitamin D increases the likelihood of contracting COVID-19 and has negative effects when combined with an underlying condition. [18].

This research sought to assess the effect of vitamin D on severely sick COVID-19 patients' outcomes.

2. Methods:

The competent committee at the Beni-Suef University Faculty of Medicine gave the research its ethical green light. Before patients were considered eligible for the current trial, their guardians had to sign an informed consent form. A personal gift helped to fund the research.

Subjects:

From January 2022 to March 2022, we conducted prospective research on 40 severely sick COVID-19 patients (COVID severity index * > 8) admitted to the ICU at Beni-Suef Isolation Chest Hospital. Without the involvement of the study's researchers, the treating physician made the choice to admit a patient to the ICU. Patients were considered eligible if they had severe COVID-19 sickness as determined by the National Early Warning Score-2 (NEWS-2) and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) confirmation [19].

Children under the age of 18, those with malignancies, or women who were pregnant were excluded. Each patient's medical history, clinical examination results, laboratory results, and lung computed tomography (CT) results for COVID-19 Recording and Documentation System (CO-RADS) categorization were all assessed. [20,21].

When patients were admitted and 48 hours later, blood samples were taken from them. A full counting and difference, CRP, ferritin, D-dimer, serum and values of vitamin D were among the laboratory tests performed. Also, the patients had regular laboratory tests for electrolytes, hepatic and renal functioning, and arterial blood gas.

PARAMETERS	3	2	1	0	1	2	3
Age (years)				≤60	61 - 64	≥65	
Male gender			yes	no			
Heart failure			yes	no			
COPD			yes	no			
Diabetes with end - organ damage			yes	no			
Chest X - Ray*				Normal or without bilateral infiltrates	Bilateral infiltrates		
Respiratory rate (breaths per minute)	≤8		9 - 11	12 - 20		21 - 24	≥25
SpO_2 (%)	≤91	92 - 93	94 - 95	≥96			
SpO_2 (%) in COPD	≤83	84 - 85	86 - 87	≥88			
Suplemental O_2	yes			no			
Systolic BP (mmHg)	≤90			90 - 219			≥220
Pulse (Beats per minute)	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Temperature (°C)	≤35		35,1 - 35,5	35,6 - 37,9	38 - 39	≥39,1	
Dyspnoea				no			
D-Dimer** (ng/ml)				≤1000	>1000		
Lymphocytes* (per mm^3)				≥1000	<1000	≤500	
Platelets* (per mm^3)				≥10000	<10000		

*** COVID – 19 severity index**

Study Findings:

The correlation between the aforementioned indicators and in-hospital death was evaluated. The connection between the examined markers and hospitalization duration, the need for mechanical ventilation, and the length of mechanical ventilation were secondary outcomes.

Statistical Analysis

IBM SPSS statistical software was utilized to summarize and analyze the retrieved data (version 25). Categories were described using frequencies, and median was utilized to summarize the numbers (range).

The Mann-Whitney test for continuous variables and the Chi-square test for categorical data were used to test the hypothesis that there is a strong connection between different parameters and clinical outcomes.

Receiver operator features were used to evaluate the prediction utility of vitamin D, and the results were shown with diagnosing accuracy metrics. p-values< 0.05 were considered statistically substantial.

3. Results:

There were 40 patients total, with an average age of 55.6 ±9.9 years and an even dispersion of the sexes. With an average of 15 days of ventilation, invasive and non-invasive mechanical ventilation was required by 62.5% of the patients.

According to Table 1, there is a statistically substantial connection between higher age, a high body temperature, and a greater APACHE II score and in-hospital mortality.

There was a link between death and male gender, the existence of diabetes mellitus, bilateral pulmonary infiltration, and heart failure despite it being statistically insignificant.

Table (1) Mortality and the baseline features of the individuals under study

Variables	Alive (no=18)	Died (no=22)	P-values
Age as mean±SD	51.8±10.8	58.7±7.9	0.025*
gender			
Females	10(50.0%)	10(50.0%)	0.525
Males	8(40.0%)	12(60.0%)	
Diabetes with EOF			
No	10(58.8%)	7(41.2%)	0.131
Yes	8(34.8%)	15(65.2%)	
HTN			
No	5(38.5%)	8(61.5%)	0.564
Yes	13(48.1%)	14(51.9%)	
Heart Failure			
No	8(53.3%)	7(46.7%)	0.412
Yes	10(40.0%)	15(60.0%)	
COPD			

No **Yes**	8(44.4%) 10(45.5%)	10(55.6%) 12(54.5%)	0.949
Vital signs Temperature HR RR Systole ≥90 mmHg <90 mmHg	 37.9±0.6 113.6±8.4 29.8±6 12(46.2%) 6(42.9%)	 38.4±0.3 117.4±12.1 30.1±3.2 14(53.8%) 8(57.1%)	 0.001* 0.264 0.768 0.842
SO_2	84.4±6	86.7±4.6	0.179
APACH II score	12.8±6.9	17.7±6.1	0.023*
bilateral lung infiltration No Yes	7(70.0%) 11(36.7%)	3(30.0%) 19(63.3%)	0.067

Table (2) shows that among non-survivors, there was no statistical substantial connection between baseline vitamin D values and in-hospital death. When the examination was repeated after 48 hours, non-survivors had a much greater amount of vitamin D.P-value = 0,007

Table 2 Relation between blood markers of the studied patients and mortality

Characteristics	Baseline			48 hours		
	Alive (no=18)	Died (no=22)	p-value	Alive (no=18)	Died (no=22)	p-value
Vit D	21.6 ± 7.6	18.8 ± 2.4	0.114	20.2 ± 5.4	16.6 ± 2.3	0.007

At baseline, serum vitamin D did not have a significant role in mortality prediction. 48 hours from admission, a considerable contribution to the predicting of mortality was made by serum vitamin D.

Table (3) showed that there was a considerable connection between death and need to mechanical ventilation, SOFA score after 48 hours and the dose of vasopressors.

variables	Alive (no=18)	Died (no=22)	P-value
Need to MV No Yes	 15(100.0%) 3(12.0%)	 0(0.0%) 22(100,0%)	 <0.001*
Days on mechanical ventilation	(no=3) 10.3±1.5	(no=22) 15.6±5.6	0.127
LOS in ICU	16.7±5.9	18.4±5.1	0.343
SOFA score after 48 hours	6.6±1.9	10.9±1.7	<0.001*
Vasopressor dose <0.1mic/Kg ≥0.1 mic/Kg	 18(100.0%) 0(0.0%)	0(0.0%) 22(100.0%)	<0.001*

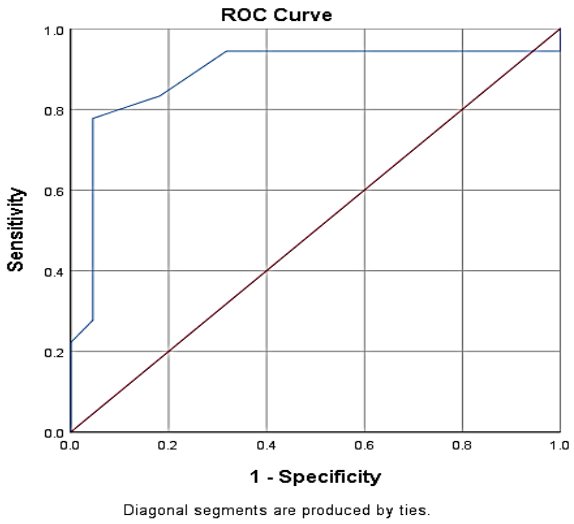

Figure (1) Receiver Operating Characteristic curve for the 48-hour death prediction from moderately increased vitamin D

Table (4) showed that At a cutoff of ≤18, the vitamin D value after 48 hours has a substantial influence in the prediction of death.

After 48 hours	Area under curve	P-values	cut off	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)

vit D	0.886	<0.001*	≤18	81.82(59.7 - 94.8)	83.33(58.6 - 96.4)	85.7(67.7 - 94.5)	78.9(60.1 - 90.3)

Table (5) showed that The duration of stay in the ICU was substantially connected positively along a straight line with baseline levels of CRP and phosphorus, but negatively with the patient's vitamin D level upon admission.

no=40		**ICU stay duration**
Age	r	0.135
	P-value	0.407
Na on admission	r	-0.112
	P-value	0.491
K on admission	r	-0.179
	P-value	0.269
Ca on admission	r	0.020
	P-value	0.902
Creat on admission	r	0.076
	P-value	0.641
PO4 on admission	r	0.387
	P-value	0.014
Mg on admission	r	-0.221
	P-value	0.170
TLC on admission	r	0.174
	P-value	0.283
PLT on admission	r	0.164
	P-value	0.312
CRP on admission	r	0.532
	P-value	<0.001
INR on admission	r	-0.064
	P-value	0.696
Ferritin on admission	r	0.014
	P-value	0.933

D- dimer on admission	r	0.132
	P-value	0.418
Vit. D. on admission	r	-0.324*
	P-value	0.042
NLR on admission	r	0.159
	P-value	0.326
AST on admission	r	-0.192
	P-value	0.235
ALT on admission	r	-0.218
	P-value	0.178
Bilirubin on admission	r	0.188
	P-value	0.245
Albumin on admission	r	0.027
	P-value	0.870
APACHE II score on admission	R	0.200
	P-value	0.216
SOFA score 48 hrs after admission	R	0.034
	P-value	0.837

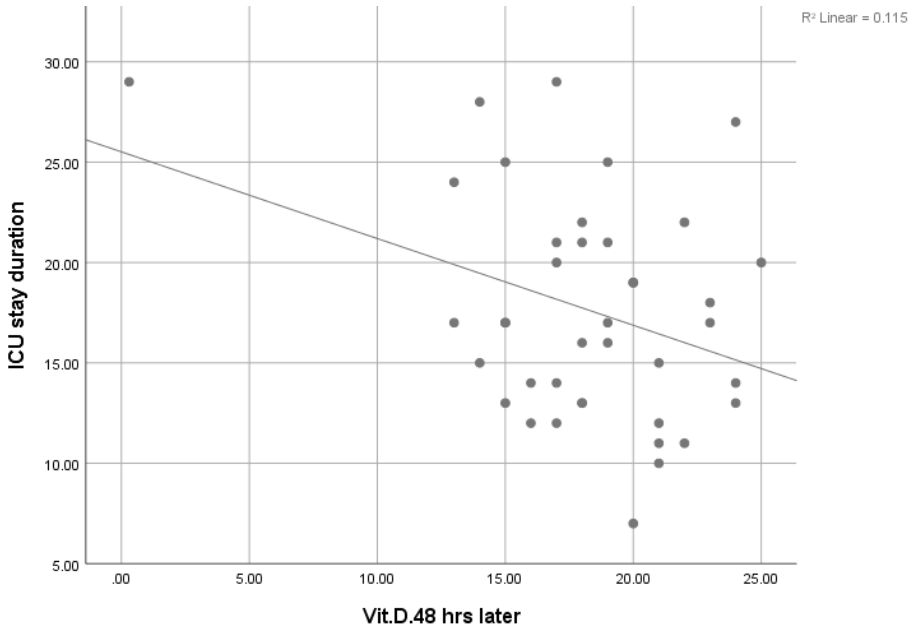

Figure (2) Correlations between length of stay in ICU and Vit.D 48hrs after admission

4. Discussion:

This study revealed no statistically substantial connection of baseline vitamin D among non-survivors. P-value=0.114 (insignificant). However,

vitamin D levels after 48 hours have a substantial role in prediction of death at a cut off ≤18 ng /mL This may be due to some factors like association with comorbidities.

Area under curve = 0.886. P-value = <0.001. Sensitivity (95%CI) = 81.82(59.7 - 94.8). Specificity (95%CI) = 83.33(58.6 - 96.4). PPV (95%CI) = 85.7(67.7 - 94.5). NPV (95%CI) = 78.9(60.1 - 90.3).

In contrast to a retrospective study, **Illie et al (2020)** conducted in 20 nations in Europe (8th April 2020) on adult patients, indicated a substantial inverse connection between median vitamin D values and the number of COVID-19 cases and deaths (p = 0.050 and.0,053, respectively) per million of the population. (22).

However, **Campi et al (2021)** Study participants were 103 in-patients with acute COVID-19 symptoms who were hospitalised to a northern Italian hospital. Their ages ranged from 66.1±14.1 years. A comparison between 206 people without SARS-CoV-2 infections and 52 subjects with moderate COVID-19 symptoms served as the control group.

During admission, IL-6 and vitamin D (25-OH vitamin D) values were evaluated with an emphasis on how the patient would fare with their respiratory condition.

Low 25OHD concentrations at hospitalization were associated with higher IL-6 values, which independently predicted the severity of respiratory failure and mortality during hospitalization **(**23,24**)**. Also, **Raharusuna et al (2020)** retrospective cohort investigation done in Indonesia government hospital (2 March-2-24 April 2020) and included 780 adult patients with mean age 54,5 years (25) . According to the study's findings, instances of older, Male patients with pre-existing illnesses and insufficient vitamin D levels had a higher probability of passing away.

Moreover, vitamin D concentrations demonstrated a significant association with COVID-19 death after controlling for covariates (age, gender, and comorbidity).

Our study suggested that, with some limitations like small sample size, Vitamin D, can be utilized as a marker of mortality in COVID-19 patients.

Also our research showed **insignificant statistical association** between mortality and presence of DM with EOF (**P-value** =

0.131), presence of HT**N** (**P-value** = 0.564) presence of COPD (**P-value** = 0.949), bilateral infiltration of lungs (**P-value** = 0.067) and heart failure (**P-value** = 0.412) ,but there was still clinical significance of association of these characteristics with mortality.

In accordance to **Shi et al. (2021)** meta-analysis study. The following significant predictors were linked to death out of a sum of 106 possible risk factors: chronic renal, pulmonary, and cardio-cerebrovascular disorders, such as heart failure, diabetes, and hypertension, a serious condition, are examples of preexisting comorbidities. As compared to individuals without comorbidities, those with any comorbidity had a 2.85-fold greater chance of dying.

Patients with persistent kidney illness, cerebrovascular illness, pulmonary illness, cardiac disease, diabetes mellitus, or hypertension had mortality risks that were, respectively, eight times, eight times, four times, three times, two times, and two times greater than those without these conditions, with a P-value < 0.001. Patients with chronic kidney illness had the greatest mortality risk. Cerebrovascular disease came in second, followed by chronic respiratory illness, heart disease, diabetes mellitus and hypertension.

Our study showed **insignificant statistical association** between presence of DM with EOF, presence of HTN, presence of COPD, bilateral infiltration of lungs, and heart failure due to some limitations as small number of patients.

Our study showed that with a mean number of days on ventilation, 62.5% of the patients in the study required mechanical ventilation. A substantial link between mortality and the requirement for mechanical ventilation as well as a substantial connection between death and the dosage of vasopressors were found after 15 days in which 55% of participants required high dosages of vasopressors. The average duration of stay in the ICU was 17.7±5.5 days, and 55% of individuals died.

5. Conclusion:

Vitamin D deficient – COVID -19 patients are more liable to severe illness and following up vitamin D levels in blood can predict mortality.

Acknowledgment:

We accept that the limited sample size and single-center design of our research, among other factors, may restrict the applicability of our results. Moreover, neither the research parameters nor the biomarkers of multiple organ failure were correlated by us.

Declarations:

Conflict of Interest: no conflicts of interest.

6. References:

1. Abdel-Ghaffar, Muhammad M., et al. "Prediction of mortality in hospitalized Egyptian patients with Coronavirus disease-2019: A multicenter retrospective study." Plos one, Vol. 17, No. 1, 2022, p.e0262348.
2. Omran, Dalia, et al. "Predictors of severity and development of critical illness of Egyptian COVID-19 patients: A multicenter study" Plos one, Vol. 16, No. 9, 2021, p. e0256203.
3. Infante, Marco, et al. "Hydroxychloroquine in the COVID-19 pandemic era: in pursuit of a rational use for prophylaxis of SARS-CoV-2 infection." Expert review of anti-infective therapy, Vol. 19, No. 1, 2021, pp. 5-16.
4. Liu, Jing, et al. "Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients." EBioMedicine, Vol. 55, 2020.
5. Huang, Chaolin, et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." The lancet, Vol. 395, No. 10223, 2020, pp. 497-06.
6. Moore, John B., and Carl H. June. "Cytokine release syndrome in severe COVID-19." Science, Vol. 368, No. 6490, 2020, pp. 473-74.
7. Ye, Qing, Bili Wang, and Jianhua Mao. "The pathogenesis and treatment of the Cytokine Storm'in COVID-19." Journal of infection, Vol. 80, No. 6, 2020, pp. 607-13.
8. Zaim, Sevim, et al. "COVID-19 and multiorgan response." Current problems in cardiology, Vol. 45, No. 8, 2020, p. 100618.
9. Zhou, Fei, et al. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." The Lancet, Vol. 395, No. 10229, 2020, pp. 1054-62.
10. Tang, Ning, et al. "Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia." Journal of thrombosis and haemostasis, Vol. 18, No. 4, 2020, 844-47.
11. Caprio, Massimiliano, et al. "Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects." Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, Vol. 22, No. 1, 2017, pp. 27
12. Fabbri, A., M. Infante, and C. Ricordi. "Editorial-Vitamin D status: a key

modulator of innate immunity and natural defense from acute viral respiratory infections." European Review for Medical Pharmacological

13. Infante, Marco, et al. "The role of vitamin D and omega-3 PUFAs in islet transplantation." Nutrients, Vol. 11, No. 12, 2019, p. 2937.
14. Charoenngam, Nipith, and Michael F. Holick. "Immunologic effects of vitamin D on human health and disease." Nutrients, Vol. 12, No. 7, 2020, p. 2097.
15. Infante, Marco, et al. "Influence of vitamin D on islet autoimmunity and beta-cell function in type 1 diabetes." Nutrients, Vol. 11, No. 9, 2019, p. 2185.
16. Holick, Michael F. "The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention." Reviews in Endocrine and Metabolic Disorders, Vol. 18, No. 2, 2017, pp. 153-65.
17. Martineau, Adrian R., and Nita G. Forouhi. "Vitamin D for COVID 19: a case to answer?." The Lancet Diabetes & Endocrinology, Vol. 8, No. 9, 2020, pp. 735-36.
18. Infante, Marco, et al. "Low vitamin D status at admission as a risk factor for poor survival in hospitalized patients with COVID-19: an Italian retrospective study." Journal of the American Nutrition Association, Vol.
19. Huespe, Iván, et al. "COVID-19 Severity Index: A predictive score for hospitalized patients." Medicina intensiva, Vol. 46, No. 2, 2022, p. 98.
20. Singer, Mervyn, et al. "The third international consensus definitions for sepsis and septic shock (Sepsis-3)." Jama, Vol. 315, No. 8, 2016, pp. 801-10
21. Prokop, Mathias, et al. "CO-RADS: a categorical CT assessment scheme for patients suspected of having COVID-19—definition and evaluation." Radiology, Vol. 296, No. 2, 2020, pp. 97-04.
22. Ilie PC, Stefanescu S, Smith, The role of vitamin D in prevention of coronavirus disease 2019 infection and mortality. Aging clin Exp Res 2020, http://dx.doi.org/10.1007/s40520-020-01570-8
23. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, et al. vitamin D sufficiency, a serum 25-hydroxyl vitamin D at least 30 ng / ml reduced risk for adverse clinical outcomes in patients with COVID-19 INFECTION. Plos one .2020 sep 25;15(9): e0239799. https://doi.org/10.1371/journal pone 0239799

24. De Smet D, De Smet K , Herroelen P, GryspeerdtS, Martens GA. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. Am J Clin Pathol. 2021; 155 (3):3818. https://doi.org/10.1093/ajcp/aqaa252.

25. Raharusum P, Priamabada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 mortality and vitamin D an Indonesian study. SSRN J 2020, http://dx.doi.org/10.2139/ssrn.3585561

26. Available online on https://doi.org/10.1186/s12879-021-06369-0