Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (Covid-2019)

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To the Editor:

The rapid spread of Covid-2019 in many areas of the world calls for preventive health measures. Although basic guidelines on infection control are recommended, treatment has remained the best choice to avert mortality. However, for the time being, there are no known vaccines for the disease. This has driven several researchers in the world to assess the effectiveness of previously used treatments for severe acute respiratory syndrome (SARS) such as lopinavir.[1] Clinical trials for these vaccines could take more time, hence, palliative drugs have been developed to alleviate the severity of the disease.

Vitamin D has been proven to reduce risk of getting common cold.[2] It also enhances cellular immunity,[3] modulates adaptive immunity,[4] and enhances expression of antioxidation-related genes.[5] Hence, several authors proposed Vitamin D supplementation to prevent and treat Covid-2019.[6,7,8] To the best of my knowledge, no clinical trials have been conducted yet to determine the potency of Vitamin D in suppressing SARS-CoV-2 strain. A statistical analysis of the association between Vitamin D levels and clinical outcomes of Covid-2019 patients has not been described. In this paper, I used multinomial logistic regression to predict clinical outcomes of patients infected with Covid-2019 based on 25-hydroxyvitamin D [25(OH)D] levels, the barometer for Vitamin D status.

Using the database of three hospitals in Southern Asian countries, I conducted a retrospective multicentre study of 212 cases with laboratory-confirmed infection of SARS-CoV-2. Data pertaining to clinical features and serum 25(OH)D levels were extracted from the medical records. No other patient information was provided to ensure confidentiality. I classified the cases as follows: (1) mild – mild clinical features without pneumonia diagnosis, (2) ordinary – confirmed pneumonia in chest computer tomography with fever and other respiratory symptoms, (3) severe

– hypoxia (at most 93% oxygen saturation) and respiratory distress or abnormal blood gas analysis results ($PaCO_2$ >50 mm Hg or PaO_2 < 0 mm Hg), and (4) critical – respiratory failure requiring intensive case monitoring. Classification was based on a previous work.[9] I also classified the vitamin D status of the cases based on their serum 25(OH)D level: (1) normal - 25(OH)D of > 30 ng/ml, (2) insufficient - 25(OH)D of 21-29 ng/ml, and (3) deficient - 25(OH)D of < 20 ng/ml. A previous report guided this classification.[10] All data pertaining to the serum 25(OH)D levels of the cases were extracted from the onset of symptoms. The hospital conducted serum 25(OH)D test, along with other clinical tests, every seven days to monitor the status of patients. For descriptive purposes, mild cases were tested approximately 3 times, slightly lower compared to original cases (4 times), severe cases (6 times), and critical cases (7 times). Pre-admission 25(OH)D measured between 7 and 365 days before hospital admission, was also taken.[11] Mean value for time the latest pre-admission 25(OH)D level was taken, was 12.65 ± 5.32 days. A total of 223 cases were originally extracted in the analysis.

To ascertain no differences between time points, a repeated measure analysis of variance (ANOVA) was used and reported no significant differences in the serum 25(OH)D level of the 212 (95%) cases. Only a small proportion of cases reported significant differences mainly during the course of hospitalization. The 212 cases were used for the final analysis and serum 25(OH)D level taken during the onset of symptoms was considered. For statistical analysis, I used Mann-Whitney U and χ^2 tests to compare differences in the clinical outcomes. Multinomial logistic regression was used to explore the association between serum 25(OH)D level and clinical outcomes of the cases. Frequency and percentage were used for categorical variables. Mean ± SD was used to report serum 25(OH)D level of the cases. A p-value below 0.01 was considered statistically significant. Ethics approval was considered exempt owing to the nature of the study

and open-access data used. All names were originally hidden by the health governing bodies to ensure patient confidentiality.

Table 1. Descriptive statistics

Variables	Overall N (%)	Clinical Outcomes				
		Mild	Ordinary	Severe	Critical	p-value
Overall N (%)	212 (100.0)	49 (23.1)	59 (27.8)	56 (26.4)	48 (22.6)	
Serum 25(OH)D, ng/ml	23.8	31.2 ± 1.08	27.4 ± 2.14	21.2 ± 1.12	17.1 ± 2.39	<0.001
Vitamin D status						
Normal	55 (25.9)	47 (85.5)	4 (7.3)	2 (3.6)	2 (3.6)	<0.001
Insufficient	80 (37.7)	1 (1.3)	35 (43.8)	23 (28.8)	21 (26.3)	
Deficient	77 (36.3)	1 (1.4)	20 (26.0)	31 (40.3)	25 (32.5)	

Table 2. Multinomial logistic regression analysis

Predictor	Mild	OR	p-value
Serum 25(OH)D, ng/ml	Ordinary	0.614	0.007
	Severe	0.126	<0.001
	Critical	0.051	<0.001

Note: OR = odds ratio associated with the effect of a one standard deviation increase in the predictor.

Of the 212 (100.0%) cases of Covid-2019, 49 (23.1%) were identified mild, 59 (27.8%) were ordinary, 56 (26.4%) were severe, and 48 (22.6%) were critical (Table 1). Mean serum 25(OH)D level was 23.8 ng/ml. Serum 25(OH)D level of cases with mild outcome was 31.2 ng/ml, 27.4 ng/ml for ordinary, 21.2 ng/ml for severe, and 17.1 ng/ml for critical. Serum 25(OH)D levels were statistically significant among clinical outcomes ($p<0.001$). A total of 55 (25.9%) cases had normal Vitamin D status, majority of which (85.5%) were identified mild. A total of 80 (37.7%) cases had insufficient Vitamin D status, majority of which (43.8%) were ordinary. Cases identified as Vitamin D-deficient were 77 (36.3%), majority of which were severe (40.3%). Vitamin D status is significantly associated with clinical outcomes ($p<0.001$). A multinomial logistic regression analysis reported that the odds of having a mild clinical outcome rather than an ordinary outcome

were approximately 1.63 times (OR=0.614, p=0.007) for each standard deviation increase in serum 25(OH)D (Table 2). Also, for each standard deviation increase in serum 25(OH)D, the odds of having a mild clinical outcome rather than a severe outcome were approximately 7.94 times (OR=0.126, p<0.001) while interestingly, the odds of having a mild clinical outcome rather than a critical outcome were approximately more than 19.61 times (OR=0.051, p<0.001).

More generally, the odds of having a mild clinical outcome increase when serum 25(OH)D level increases. Alternatively, the odds of having a critical outcome increase when serum 25(OH)D level decreases. This means that serum 25(OH)D level in the body could account for the clinical outcomes of the patients infected with Covid-2019. An increase in serum 25(OH)D level in the body could either improve clinical outcomes or mitigate worst (severe to critical) outcomes. On the other hand, a decrease in serum 25(OH)D level in the body could worsen clinical outcomes of Covid-2019 patients. In this case, Vitamin D supplementation may play an important role to raise 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the biologically active form of Vitamin D in the blood.

In conclusion, this study provides substantial information to clinicians and health policy-makers. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Covid-2019 based on increasing odds ratio of having a mild outcome when serum 25(OH)D level increases. Further research may conduct randomized controlled trials and large population studies to evaluate this recommendation.

Declaration of Competing Interests

The author declares no conflict of interest.

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References

[1] Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., ... & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*.

[2] Rondanelli, M., Miccono, A., Lamburghini, S., Avanzato, I., Riva, A., Allegrini, P., ... & Perna, S. (2018). Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and Echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—Practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. *Evidence-Based Complementary and Alternative Medicine*, *2018*.

[3] Cantorna, M. T. (2010). Mechanisms underlying the effect of vitamin D on the immune system. *Proceedings of the Nutrition Society*, *69*(3), 286-289.

[4] Sharifi, A., Vahedi, H., Nedjat, S., Rafiei, H., & Hosseinzadeh-Attar, M. J. (2019). Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. *Apmis*, *127*(10), 681-687.

[5] Lei, G. S., Zhang, C., Cheng, B. H., & Lee, C. H. (2017). Mechanisms of action of vitamin D as supplemental therapy for Pneumocystis pneumonia. *Antimicrobial agents and chemotherapy*, *61*(10), e01226-17.

[6] Wimalawansa, S. J. (2020). Global epidemic of coronavirus--COVID-19: What we can do to minimize risks. *European Journal of Biomedical*, *7*(3), 432-438.

[7] Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., & Bhattoa, H. P. (2020). Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, *12*(4), 988.

[8] Braiman, M. (2020). Latitude Dependence of the COVID-19 Mortality Rate—A Possible Relationship to Vitamin D Deficiency?. *Available at SSRN 3561958*.

[9] Wang, Y., Liu, Y., Liu, L., Wang, X., Luo, N., & Ling, L. (2020). Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. *The Journal of infectious diseases*.

[10] Holick, M. F. (2009). Vitamin D status: measurement, interpretation, and clinical application. *Annals of epidemiology*, *19*(2), 73-78.

[11] Thickett, D. R., Moromizato, T., Litonjua, A. A., Amrein, K., Quraishi, S. A., Lee-Sarwar, K. A., ... & Giovannucci, E. (2015). Association between prehospital vitamin D status and incident acute respiratory failure in critically ill patients: a retrospective cohort study. BMJ open respiratory research, 2(1), e000074.