Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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KEY FINDINGS:

- Majority of the COVID-19 cases with insufficient and deficient Vitamin D status died.
- The odds of death was higher in older and male cases with pre-existing condition and below normal Vitamin D levels.
- When controlling for age, sex, and comorbidity, Vitamin D status is strongly associated with COVID-19 mortality.
- Randomized controlled trials are warranted to investigate the role of vitamin D supplementation on COVID-19 outcomes and to establish the underlying mechanisms.

ABSTRACT

This is a retrospective cohort study which included two cohorts (active and expired) of 780 cases with laboratory-confirmed infection of SARS-CoV-2 in Indonesia. Age, sex, co-morbidity, Vitamin D status, and disease outcome (mortality) were extracted from electronic medical records. The aim was to determine patterns of mortality and associated factors, with a special focus on Vitamin D status. Results revealed that majority of the death cases were male and older and had pre-existing condition and below normal Vitamin D serum level. Univariate analysis revealed that older and male cases with pre-existing condition and below normal Vitamin D levels were associated with increasing odds of death. When controlling for age, sex, and comorbidity, Vitamin D status is strongly associated with COVID-19 mortality outcome of cases.

INTRODUCTION

The Coronavirus-2019 (COVID-19) pandemic remains a pressing problem in the world and will continually surface as more than 30 different mutations of the disease strain, severe acute respiratory syndrome-coronavirus (SARS-CoV-2), were detected from the latest study in China.[1] With the increasing number of novel strains, researchers across the world are driven to conduct clinical trials for potential anti-viral treatments. However, the likelihood of potential vaccines for the disease went down, due to more evidence debuting previous claims on the efficacy of the tested drugs. Scientists continue to search for effective treatments, with efforts focused on several existing drugs.

Vitamin D has been proven to enhance expression of anti-oxidation-related genes, modulates adaptive immunity, and improves cellular immunity.[2,3,4,5]With the remarkable potential of Vitamin D, several researchers proposed Vitamin D supplementation could possibly treat COVID-19 or reduce severity, at least.[6,7,8,9,10,11,12]

In a previous report, a significant association between vitamin D status and severity of COVID-19 disease has been documented in Southeast Asia.[11] The report suggests that serum 25(OH)D level was lowest in critical cases, but highest in mild cases which thereby increase the odds of having a mild clinical outcome rather than a critical outcome by approximately 19.61 times. The result further fortified initial hypotheses of Vitamin D proponents that a decrease in serum 25(OH)D level in the body could worsen clinical outcomes of COVID-19 patients while an

increase in serum 25(OH)D level in the body could either mitigate worst outcome or improve clinical outcomes.

Existing literature provides evidence that pre-hospitalization serum 25(OH)D is linked to outcomes of respiratory diseases. Using cross-sectional data from 6789 participants in the nationwide 1958 British birth cohort who had measurements of 25(OH)D, Berry et al.[13] reported that vitamin D status had a linear relationship with respiratory infections and lung function. Pre-admission 25(OH)D deficiency was also predictive for short-term and long-term mortality.[14,15]

This study has focused on identifying patterns of mortality among patients infected with Covid-19 and the possible association between serum 25(OH)D level and mortality outcomes. In this study, age, sex, and co-morbidity were added as factors and an outcome variable, mortality, was analyzed to further provide strong evidence of Vitamin D potency for SARS-CoV-2.

METHODS

Study Design and Participants

This is a retrospective cohort study which included two cohorts (active and expired) of 780 cases with laboratory-confirmed infection of SARS-CoV-2. Data between March 2, 2020 (start of outbreak in Indonesia) and April 24, 2020 were obtained from medical records of Indonesia government hospitals. The requirement for informed consent was waived by the Ethics Commission. To ensure anonymity, all names were preserved

throughout the analysis.

Data Collection

Age, sex, co-morbidity, Vitamin D status, and disease outcome (mortality) were extracted from electronic medical records. Co-morbidity status was classified as with or without pre-existing condition.

For Vitamin D status, cases were classified based on their serum 25(OH)D levels: (1) normal - serum 25(OH)D of > 30 ng/ml, (2) insufficient - serum 25(OH)D of 21-29 ng/ml, and (3) deficient - serum 25(OH)D of < 20 ng/ml. This classification was based on existing literature.[16] The pre-admission serum 25(OH)D levels were considered for the analysis. Serum 25(OH)D level was checked by two physicians based on the available clinical data of the patients.

Statistical Analysis

Analysis was carried out using SPSS 21.0 statistical software. Mean was used for continuous variable (age), while frequency and percentage were employed for categorical variables. To compare differences in the outcomes, Mann-Whitney U and χ^2 tests were used. Meanwhile, univariate logistics regression was used to determine the association between each predictor variable and mortality outcome. The odds ratio (OR) associated with the effect of a one standard deviation increase in the predictor was used in the interpretation of data. To determine the association of Vitamin D status and mortality outcome, all ORs were adjusted

for age, sex, and comorbidity using a generalized linear model. A p-value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Descriptive Statistics

The demographic and clinical characteristics of two cohorts (active and expired) are presented (**Table 1**). Mean overall age was 54.5 years, mean age for expired cases was 65.2 years, higher compared to active cases (46.3 years). Of the 780 sample, majority (58.8%) aged below 50 years, most of the them (83.0%) are still admitted in the hospital. Of the 321 samples aged 50 years and above, majority (66.6%) died due to the disease. Females (51.3%) outnumbered males (48.7%); however, there were more male cases who died (66.6%) than female (33.4%). Patients with existing condition (84.9%) comprised majority of the death cases. Interestingly, majority of the cases had normal Vitamin D status (49.7%), most of them (93.0%) are still hospitalized. Of the 213 cases with insufficient Vitamin D status, majority (49.1%) died. The same distribution was observed in Vitamin D deficient cases where majority (46.7%) died due to the disease.

A total of 179 cases had Vitamin D deficiency (Vitamin D < 20 ng/ml), mean level of serum 25(OH)D and mean age for this group were 18.2 ± 0.6 ng/ml and 66.9 ± 13.8 years, respectively (**Table 2**). 213 cases had Vitamin D insufficiency (Vitamin D 20-30 ng/ml), mean level of serum 25(OH)D and mean age for this group were 26.7 ± 1.3 ng/ml and 62.9 ± 14.7 years, respectively. 388 cases

had normal Vitamin D levels (Vitamin D > 30 ng/ml), mean level of serum 25(OH)D and mean age for this group were 32.2 ± 1.2 ng/ml and 46.6 ± 12.6 years, respectively. 80.0% of Vitamin D deficient cases had pre-existing conditions (comorbidity). 73.8% of Vitamin D insufficient cases had pre-existing conditions (comorbidity). 18.8% of cases with normal Vitamin D levels had pre-existing conditions (comorbidity). 98.9% of Vitamin D deficient cases died while only 1.1% of them were active cases. 87.8% of Vitamin D insufficient cases died while only 12.2% of them were active cases. Only 4.1% of cases with normal Vitamin D levels died while 95.9% of them were active cases.

Univariate Analysis

Each predictor was separately analyzed using univariate logistic regression (**Table 2**). Older cases (50 years and above) were approximately 10.45 times more likely to die than younger cases (at most 50 years) (OR=10.45; p<0.001). Male cases were approximately 5.73 times more likely to die from the disease than female cases (OR=5.73; p<0.001). Meanwhile, cases with pre-existing condition had increased odds of mortality compared to cases without (OR=11.24; p<0.001). With reference to normal cases, Vitamin D insufficient cases were approximately 12.55 times more likely to die (OR=12.55; p<0.001) while Vitamin D deficient cases were approximately 19.12 times more likely to die from the disease (OR=19.12; p<0.001).

Generalized Linear Model

To control for possible confounding of age, sex, and comorbidity on the association of Vitamin D status and mortality outcome, a generalized linear model was employed (**Table 3**). After accounting for these variables in the model, a significant association has been obtained between Vitamin D status and mortality. In particular, the odds of death was higher in cases with insufficient Vitamin D status (OR=7.63; $p<0.001$). When compared to cases with normal Vitamin D status, death was approximately 10.12 times more likely for Vitamin D deficient cases (OR=10.12; $p<0.001$).

Table 1. Demographic and clinical characteristics of sample

Variables	Total (N=780)	Expired (N=380)	Active (N=400)	p-value
Age, mean	54.5	65.2	46.3	
< 50 years	459 (58.8%)	127 (33.4%)	332 (83.0%)	<0.001
≥ 50 years	321 (41.2%)	253 (66.6%)	68 (17.0%)	
Sex				
Female	400 (51.3%)	128 (33.4%)	332 (83.0%)	<0.001
Male	380 (48.7%)	252 (66.6%)	68 (17.0%)	
Comorbidity				
Yes	383 (49.1%)	323 (84.9%)	60 (15.0%)	<0.001
No	397 (50.9%)	57 (15.1%)	340 (85.0%)	
Vitamin D Status				
Normal	388 (49.7%)	16 (4.2%)	372 (93.0%)	<0.001
Insufficient	213 (27.3%)	187 (49.1%)	26 (6.5%)	
Deficient	179 (23.0%)	177 (46.7%)	2 (0.5%)	

Table 2. Dynamics of Vitamin D status

	Vitamin D < 20 ng/ml (18.2 ± 0.6)	Vitamin D 20-30 ng/ml (26.7 ± 1.3)	Vitamin D > 30 ng/ml (32.2 ± 1.2)
Overall, N	179	213	388
Mean age	66.9 ± 13.8	62.9 ± 14.7	46.6 ± 12.6
Comorbidity, %	80.0	73.8	18.8
Death, %	98.9	87.8	4.1
Active, %	1.1	12.2	95.9

Table 3. Univariate analysis for factors associated with mortality

Variables	OR	p-value
Age, mean		
< 50 years	-	
≥ 50 years	10.45	<0.001
Sex		
Female	-	
Male	5.73	<0.001
Comorbidity		
Yes	11.24	<0.001
No	-	
Vitamin D Status		
Normal	-	
Insufficient	12.55	<0.001
Deficient	19.12	<0.001

Table 4. Association between Vitamin D status and mortality (adjusted for age, sex, and comorbidity)

Variable	OR	p-value
Vitamin D Status		
Normal	-	
Insufficient	7.63	<0.001
Deficient	10.12	<0.001

CONCLUSION

To the best of the researchers' knowledge, this is the first retrospective study which determines the association of Vitamin D status and COVID-19 mortality outcome. Older and male cases with pre-existing condition and below normal Vitamin D levels were associated with increasing odds of death. When controlling for age, sex, and comorbidity, Vitamin D status is strongly associated with COVID-19 mortality outcome of cases. Randomized controlled trials are warranted to investigate the role of vitamin D supplementation on COVID-19 outcomes and to establish the underlying mechanisms.

REFERENCES

[1] **Hangping Yao, Xiangyun Lu, Qiong Chen, Kaijin Xu, Yu Chen, Linfang Cheng, Fumin Liu, Zhigang Wu, Haibo Wu, Changzhong Jin, Min Zheng, Nanping Wu, Chao Jiang, Lanjuan Li.** Patient-derived mutations impact pathogenicity of SARS-CoV-2. doi: 10.1101/2020.04.14.20060160

[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] **Brown RA, Sarkar A (2020).** Vitamin D deficiency: a factor in COVID-19, progression, severity and mortality? – An urgent call for research. MitoFit Preprint Arch doi: 10.26124/mitofit:200001

[9] **Ilie, P., Stefanescu, S., Smith, L. (2020).** The role of Vitamin D in the prevention of Coronavirus Disease 2019 infection and mortality. Square Research. doi:10.21203/rs.3.rs-21211/v1.

[10] **Grant, W. (2020).** Re: Preventing a covid-19 pandemic: Can vitamin D supplementation reduce the spread of COVID-19? Try first with health care workers and first responders. doi: 10.1136/bmj.m810 https://www.bmj.com/content/368/bmj.m810/rr-42

[11] **Alipio, M. (2020).** Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019). Available at SSRN: https://ssrn.com/abstract=3571484 or http://dx.doi.org/10.2139/ssrn.3571484

[12] **Rhodes, J.M., Subramanian, S., Laird, E. and Anne Kenny, R. (2020),** Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North – supports vitamin D as a factor determining severity. Aliment Pharmacol Ther. Accepted Author Manuscript. doi:10.1111/apt.15777

[13] **Berry, D. J., Hesketh, K., Power, C., & Hyppönen, E. (2011).** Vitamin D status has a linear association with seasonal infections and lung function in British adults. British Journal of Nutrition, 106(9), 1433-1440.

[14] **Braun, A., Chang, D., Mahadevappa, K., Gibbons, F. K., Liu, Y., Giovannucci, E., & Christopher, K. B. (2011).** Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Critical care medicine, 39(4), 671.

[15] **Watkins, R. R., Lemonovich, T. L., & Salata, R. A. (2015).** An update

on the association of vitamin D deficiency with common infectious diseases. Canadian journal of physiology and pharmacology, 93(5), 363-368.

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