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# Relationships between comorbidities and vitamin D intake with COVID-19 severity

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## Abstract

**Background**: Vitamin D is a nutrient/hormone-like vitamin involved in immune regulation, which, in turn, affects morbidity and mortality rates, including in coronavirus disease 2019 (COVID-19). Vitamin D strengthens both specific and nonspecific immunity and modulates the body's response to infection.

**Objective:** This study aims to determine the association between comorbidities and vitamin D intake with the severity of COVID-19.

**Methods:** The study is a cross-sectional observational study with a sample comprised of 66 people, ages 19 to 58, receiving treatment for COVID-19 at Pasar Rebo District Hospital. The primary data were collected via a questionnaire administered via the WhatsApp application or through direct interviews, encompassing variables such as age, gender, comorbidity, and vitamin D intake. The Vitamin D Dietary Intake Questionnaire was conducted using the Food Frequency Questionnaire (FFQ). Vitamin D intake is categorized into two groups: low (<600 IU/day) and adequate (≥600-4,000 IU/day). Comorbidities are other illnesses that a person has, such as asthma, high blood pressure, diabetes, or heart disease. The severity of COVID-19 is an accordance with the criteria set by the Indonesian Society of Internal Medicine. Statistical analysis used SPSS version 22 to analyze univariate data and Fisher's exact test for bivariate analysis with a significance limit of $p < 0.05$.

**Results:** A total of 25.8% of the subjects had comorbidities, 62.1% experienced low vitamin D intake, and 53% experienced mild COVID-19 symptoms. The severity of COVID-19 cases does not correlate with age or gender. The severity of COVID-19 cases was significantly associated with comorbidities (p=0.001) and vitamin D intake (p=0.021).

**Conclusion:** An association was observed between vitamin D intake, comorbidities, and the severity of COVID-19.

**Keywords:** vitamin D, COVID-19, comorbidities

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## Introduction

The World Health Organization has declared an international emergency due to the devastation caused by the COVID-19 epidemic.[1] An RNA virus, known as a coronavirus, carries small particles and can spread through droplets. The infection mainly occurs in animals, but currently, transmission is primarily human-to-human, and the spread is very aggressive.[2] Many factors, including the host, virus, and environment, can influence COVID-19 severity. Age can influence the severity of different cases.[3] Diet is another independent risk factor for developing serious infections. It is critical to consume healthy, fresh, and nutritious foods while avoiding diets high in saturated fats, sugar, and refined carbohydrates. Vitamin D deficiency may influence comorbidities and susceptibility to infectious disease.[3]

The immune system of the body greatly influences an individual's susceptibility, morbidity, and mortality from COVID-19, as with other viral diseases. One factor that can influence the body's immune response is vitamin D.[4] Vitamin D can reduce the risk of viral infection through a number of approaches, including strengthening both specific and nonspecific immunity and modulating the body's response to an infection. Vitamin D also plays a role in adaptive and innate immune responses, which are essential for inhibiting cytokine storms and reducing pro-inflammation responses.[4,5] Vitamin D deficiency has been hypothesized contributes to the occurrence of acute respiratory distress syndrome (ARDS) (SARS-CoV-2).[5] As previously explained, the objective of this study was to determine whether vitamin D intake and comorbidities were associated with COVID-19 severity.

## Methods

This is an analytical observational study with a cross-sectional design. The research was conducted at Pasar Rebo District Hospital from November to December 2021. The research sample came from the medical records of 66 subjects inpatients aged 19-58 years diagnosed with COVID-19 who met the inclusion criteria. The inclusion criteria are as follows: patients diagnosed with COVID-19 by PCR test. The exclusion criteria are patients who are still under treatment in the hospital and patients who died during treatment. Primary data were collected through a questionnaire completed via the WhatsApp application, which included age, gender, and vitamin D intake, while comorbidities and COVID-19 severity were taken from medical records. Direct interviews are conducted when WhatsApp responses are unclear. Comorbidities are accompanying illnesses (asthma, hypertension, diabetes, heart disease) that describe the patient's condition apart from the primary illness, namely COVID-19, recorded in the medical record; "yes" indicates one or more comorbidities. The vitamin D dietary intake questionnaire was conducted using the Food Frequency Questionnaire (FFQ) past month. The vitamin D intake is categorized into two groups based on the Minister of Health Regulation Number 28 of 2019 concerning Nutritional Adequacy Rates; low (<600 IU/day) and adequate (≥600 - 4,000 IU/day). The severity of COVID-19 is an accordance with the criteria set by the Indonesian Society of Internal Medicine.[6] The severity of COVID-19 is determined by the patient's worst condition during hospital treatment.

To process and analyze the data, the Statistical Package for the Social Sciences (SPSS) 22.0 was used. Categorical variables were expressed as frequencies and percentages. Intergroup comparison was conducted using Fisher's exact test because the expected

count of less than 5 is more than 20%. To determine statistical significance, a p-value of less than 0.05 was used. Multivariate analysis was not considered due to insufficient data.

## Results

The Research Ethics Commission of Universitas Trisakti, with number 104/KER-FK/IX/2021, declared this research to have passed the ethical test. After processing and counting the respondents, we analyzed 66 subjects, yielding a response rate of 100%. No data was missing or excluded from the analysis.

**Table 1.** Subject characteristics (N = 66)

| Variables | Frequencies | |
|---|---|---|
| | N | (%) |
| Age | | |
| 19 – 48 years old | 49 | 74.2 |
| 49 – 58 years old | 17 | 25.8 |
| Sex | | |
| Men | 36 | 54.5 |
| Women | 30 | 45.5 |
| Comorbidities | | |
| Yes | 17 | 25.8 |
| No | 49 | 74.2 |
| Vitamin D intakes | | |
| Low | 41 | 62.1 |
| Adequate | 25 | 37.9 |
| Severity of COVID-19 cases | | |
| Asymtomatic | 10 | 15.2 |
| Mild | 35 | 53 |
| Moderate | 3 | 4.5 |
| Severe | 12 | 18.2 |
| Critical | 6 | 9.1 |

**Table 1** displays the characteristics of the largest age group, the 19-48-year-olds, who account for 74.2% of the subjects. Most subjects were male (54.5%), and 74.2% of research subjects did not have comorbidities. The group with the highest vitamin D intake was the one with an insufficient intake, accounting for 62.1%. The most severe category of COVID-19 cases is the mild group, at 53%.

In **Table 2**, according to statistical tests, there was no significant association between age (p=0.064) and gender (p=0.791) and the severity of COVID-19 cases. Subjects with comorbidities had higher COVID-19 severity, this trend was evident in the statistical analysis, which showed a significant association (p=0.001). The group with the lowest vitamin D intake experienced the mildest symptoms of COVID-19, where the analysis showed a significant association between vitamin D intake and COVID-19 severity (p=0.021).

**Table 2.** Characteristics of subjects and vitamin D intake with severe COVID-19 cases

| Variables | Severity of COVID-19 | | | | | | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Asymptomatic | % | Mild | % | Moderate | % | Severe | % | Critical | % | |
| Age | | | | | | | | | | | |
| 19 – 48 y.o | 9 | 18.4 | 26 | 53.1 | 0 | 0 | 9 | 18.4 | 5 | 10.2 | 0.064 |
| 49 – 58 y.o | 1 | 5.9 | 9 | 52.9 | 3 | 17.6 | 3 | 17.6 | 1 | 5.9 | |
| Sex | | | | | | | | | | | |
| Men | 7 | 19.4 | 19 | 52.8 | 2 | 5.6 | 5 | 13.9 | 3 | 8.3 | 0.791 |
| Women | 3 | 10 | 16 | 53.3 | 1 | 3.3 | 7 | 23.3 | 3 | 10 | |
| Comorbidities | | | | | | | | | | | |
| Yes | 0 | 0 | 3 | 17.6 | 2 | 11.8 | 6 | 35.3 | 6 | 35.3 | 0.001* |
| No | 10 | 20.4 | 32 | 65.3 | 1 | 2 | 6 | 12.2 | 0 | 0 | |
| Vitamin D intakes | | | | | | | | | | | |
| Low | 2 | 4.9 | 26 | 63.4 | 1 | 2.4 | 8 | 19.5 | 4 | 9.8 | 0.021* |
| Adequate | 8 | 32 | 9 | 36 | 2 | 8 | 4 | 16 | 2 | 8 | |

Fisher's exact test; *p<0.05

## Discussion

The largest group of subjects aged 19 – 48 years was 74.2%; this is also the same as the percentage of subjects with no cormobidities. Several factors can contribute to the high percentage of non-comorbidities in the 19-48-year-old group. Diabetes is typically diagnosed at age ≥40 years[7-9], as well as several reports, show that the presence of early-onset hypertension (onset at age ≤55 years) is lower[10].

Indonesia is a tropical country, yet many of its citizens have low vitamin D levels because they tend to avoid direct sunlight and don't eat enough vitamin D-rich foods. Fish oil, liver, and seafish like mackerel, salmon, sardines, and tuna are high sources of vitamin D.[11] In addition, vitamin D fortifies many foods, particularly dairy products and cereals.[11] However, in Indonesia, vitamin D intake is generally obtained from eggs and freshwater fish rather than seafish.[12] The FFQ used to analyze vitamin D intake included both dietary vitamin D and supplement use. Unfortunately, this questionnaire did not ask about sun exposure, leaving it unmeasured.

The body's immune system weakens with age, increasing the likelihood of infection and making it more challenging for individuals of that age to combat infections.[13] Based on statistical tests, there is no association between age and the severity of COVID-19 cases (p = 0.064), similar to Betsy Szeto et al.,[14] research. This also implies that individuals of all ages are susceptible to severe COVID-19. Younger children, who often have close contact with peers, can easily transmit the virus in school settings, while adults may spread it in workplaces or social gatherings. Older individuals, particularly in communal living environments, are at risk of rapid transmission due to shared spaces and activities. Even though it is risky, individuals can prevent it by following standard health protocols.[15]

Aging is linked to a variety of morbidities. As protective immunity deteriorates, older people become susceptible to infections and inflammatory diseases.[16] Older people are far more likely to make autoantibodies.[17] Essentially, immunological aging correlates with diminishing protective immunity alongside a rising prevalence of inflammatory

diseases. This, in turn, can lead to an increased risk of developing more serious illnesses. Therefore, it is important to take preventive measures to reduce the risk of age-related diseases. The absence of a correlation between age and COVID-19 severity may be due to the study participants' young age.

Different immunological responses to infection have at least partially contributed to the complexity of sex differences.[18] Males have more frequently experienced severe outcomes and deaths from COVID-19 than females, according to several studies.[19] Multivariate analysis, however, showed females experienced more severe systemic and total symptoms than males.[20] Numerous prior studies have assessed sex disparities in clinical outcomes among hospitalized or severely ill COVID-19 patients.[21] In contrast to previous research, this study found no association between gender and COVID-19 case severity ($p = 0.753$).

The study results showed a significant association between comorbidities (asthma, hypertension, DM, heart disease) and COVID-19 severity ($p = 0.001$). Felly Philipus Senewe et al.,[22] research revealed a significant relationship between comorbidities and COVID-19 cases (p-value = 0.001), indicating a correlation between the respondent's comorbidities and COVID-19 case severity. Comorbidities can influence COVID-19 progression and cause more severe organ damage. For example, individuals who experience low-grade inflammation due to hypertension, diabetes mellitus, and chronic kidney disease can influence the severity of COVID-19 cases due to a systemic inflammatory process with multiorgan involvement.[23]

The severity of COVID-19 cases was statistically significantly correlated with vitamin D intake ($p = 0.021$). The FFQ used in this study to analyze vitamin D intake includes data on intake from food and supplementation. Generally, the research discussed focuses on vitamin D intake from supplementation. Vitamin D supplementation helps lower the risk of death in Covid patients (OR: 0.48; 95% CI: 0.346–0.664; $p < 0.001$). Additionally, it was also observed that supplementation decreased the need for mechanical ventilation (OR: 0.54; 95% CI: 0.411–0.708; $p < 0.001$) and intensive care (OR: 0.35; 95% CI: 0.28–0.44; $p < 0.001$).[24]

Another meta-analysis of nine studies involving 870 participants revealed that vitamin D intake was linked to a decreased risk of death (RR: 0.76; 95% CI 0.60–0.97).[25] Additionally, other meta-analyses demonstrated a favorable impact of vitamin D3 supplementation on ICU admission (RR: 0.73; 95% CI: 0.57–0.95; $p = 0.02$) and COVID-19-related patient mortality (RR: 0.56; 95% CI: 0.34–0.91; $p = 0.02$).[26] In contrast to earlier research, a meta-analysis of eight randomized clinical trials (RCTs) revealed that giving vitamin D to COVID-19 patients did not significantly alter morbidity (OR: 0.50, 95% CI: 0.13–1.96).[27]

Vitamin D has different mechanisms for dealing with the risk of viral infections, such as COVID-19. COVID-19 has the hallmarks of a severe infection, namely a cytokine storm. Cytokine storms can trigger individual immune responses to inflammatory pathogens, leading to multiple organ failure and more severe cases of COVID-19.[28,29] Vitamin D has immunomodulatory properties and increases innate cellular immunity by reducing cytokine storms induced by the innate immune system, thereby affecting the body's defenses. The innate immune system produces pro-inflammatory and anti-inflammatory cytokines in response to bacterial and viral infections. The innate immune system supports innate immunity by producing several antimicrobial peptides (cathelicidins, defensins, and IL-37). Additionally, vitamin D modulates the production

and release of proinflammatory cytokines like IL-6, TNF-alpha, and interferon-gamma and controls responses mediated by Th lymphocytes.[30]

Vitamin D deficiency is linked with metabolic disorders, autoimmune diseases, and infections. Numerous research studies highlight the association between vitamin D deficiency and an elevated risk of respiratory tract infections. Furthermore, vitamin D deficiency is prevalent in critically ill patients and has been linked with more serious illnesses. The high number of severe COVID-19 patients with inadequate vitamin D levels suggests a link between low vitamin D levels and poor outcomes. Taking vitamin D might reduce the severity of the disease and increase the chances of recovery.[27]

Limitations of this study include the lack of control for potential confounding factors. Two potentially important confounding factors are subjects' cycle threshold (CT) values and sun exposure. Excluding patients who died during treatment and analyzing comorbidities as a single group may introduce bias. It must also be understood that dietary intake may not reflect serum vitamin D status. This study is a cross-sectional study, which means it cannot establish causality and primarily supports hypothesis formation.

## Conclusion

Comorbidities and vitamin D intake are associated with the severity of COVID-19 infection. It is recommended that the initial assessment of COVID-19 patients include identification of comorbidities. Further research on the impact of vitamin D intake, adjusting for confounding variables, may be necessary to minimize the severity of COVID-19.

## Conflict of interest

The authors declared no conflict of interest regarding this article.

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## Open Access



## Author Contributions

MR: Conceptualization, data acquisition, formal analysis, interpretation of results, drafting the manuscript, and final approval of the version to be published; VS: Conceptualization, supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published.

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