THE EFFECT OF VITAMIN D, VITAMIN C, AND MULTIVITAMIN ON LENGTH OF STAY AND CLINICAL OUTCOME OF COVID-19 PATIENTS AT BANTUL GENERAL HOSPITAL, YOGYAKARTA

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ABSTRACT

Background: Vitamin and multivitamins placed as supportive role in COVID-19 pharmacology therapy. They worked through several mechanisms such immuno-modulatory, antioxidant, and anti-inflammatory. Clinical evidence on their positive impact on clinical improvement was remain limited. The aims of this study to describe the use of vitamins and multivitamins and to analyse the association between vitamins or multivitamins against length of stay and clinical outcome.

Subjects and Methods: Study design was using analytical observational, cross-sectional, and retrospective approach. Research was taken in Bantul General Hospital Yogyakarta using consecutive sampling method from medical record data of COVID-19 inpatients from March 2020 to May 2021. The independent variables is vitamins or multivitamins. The dependent variables is length of stay and clinical outcome. Bivariate analysis was using Chi square test.

Results: Total of 214 patients met the inclusion criteria. Majority numbers were found in male group (53.70%), 45-64 years old (50.90%), moderate level (80.40%), and having comorbid (89.30%). Pneumonia, diabetes, and hypertension were the common morbidities existed in this study. Most of patients suffered fever, dyspnea, and fever as their symptoms during the infection. Vitamin D, vitamin C, and multivitamin ranked as three biggest consumption supplements by 29.15%, 26.86%, and 23.50%, respectively. There was no association found on vitamin C and vitamin D utility to length of stay and clinical outcome. Meanwhile, there was significant association between multivitamin and clinical outcome (OR= 1.14; CI95%= 1.08-1.20; P=0.029).

Conclusion: There was no association discovered between vitamin D and vitamin C against length of stay and clinical outcome in this study whereas the only meaningful association found on the use of multivitamin to better improvement on clinical outcome marked by healed. The implication of this study was to suggest the application of multivitamin among COVID-19 patients in order to earn better outcome.

Keywords: vitamin C, vitamin D, multivitamin, COVID-19, outcome.

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BACKGROUND

World Health Organization (WHO) announced COVID-19 as pandemic on March 2020. This situation began by the spread of the disease in China since Desember 2019 and has increased 13-fold around the world (WHO, 2020). Pharmacological therapy on COVID-19 was on their pursuit to discover the proper treatment. In Indonesia, COVID-19 Treatment Protocol Guideline recommended several medications including vitamin C,

vitamin D, antivirus, antibiotic, and other officially registered traditional supplements (Indonesian Ministry of Health, 2020). Various micronutrients consisted vitamins showed supportive function in immune system and in minimizing the risk of respiratory infection. The consumption of multi-vitamin rose during COVID-19 era compared to previous time in Saudi Arabian population (Bakhshwin and Bakhshwin, 2021). Vitamin C was believed inhibit the activation of a main proinflammatory transcription factor, NFkB, and also to prevent the production of Interleukin-6 (IL-6) and Tumor necrosis factor alpha (TNF-α) (Dewi et al., 2021). In other hand, vitamin D assumed to have direct inhibition effect on viral replication and anti-inflammatory or immunemo-dulatory way (Ali, 2020). However, clinical evidence on support role of vitamins and minerals were still limited (Louca et al., 2021).

SUBJECTS AND METHOD

1. Study design
An analytical observational, cross-sectional, and retrospective were using in this study. Research venue was in Bantul General Hospital, Yogyakarta Province and using secondary data through medical data record.

2. Population and Sample
The number of participants was 214, determined by using Slovin formula. Sampling method was using purposive sampling.

Inclusion criteria were adult inpatients (≥18 years old) confirmed positive COVID-19 by Polymerase Chain Reaction (PCR) test result from March 2020 until May 2021, with or without comorbid, received vitamin C, vitamin D, and/ or multivitamin as one of pharmacological therapy. The exclusion criteria were pregnant woman and hospital discharge status requested by patients themselves.

3. Study Variables
The independent variables is vitamins or multivitamins. The dependent variables is length of stay and clinical outcome

4. Operational Definition of Variables
Vitamins or multivitamins defined by vitamin D, vitamin C, multivitamin, zinc, curcuma, and folic acid that consumed by COVID-19 patients.

Length of stay defined by the duration of patient's stay in hospital counted from admission day until hospital discharge day. Secondary outcome was determined by clinical outcome.

Clinical outcome interpreted as the status of COVID-19 patients by the time of hospital discharge. They were divided into healed and death. Healed defined improvement condition in a patient with or without negative result of PCR test and confirmed by medical doctor. Clinical outcome was divided into two characteristics. Primary outcome was length of stay categorized as ≤ 7 days and > 7 days.

5. Data analysis
Univariate analysis was used to describe patient's demographics and medication characteristics, represented as frequencies and percentages. Bivariate analysis was used to analyze the association between medications use (vitamin C, vitamin D, and multi-vitamin) towards length of stay and clinical outcome by Chi-square test.

Data was processed by SPSS version 22.

6. Research Ethics

Ethical approval was issued by Ethic Committee of University of Jenderal Achmad Yani with approval number of Skep/0100/KEPK/V/2020.

1. Patient's Demographics

Data in Table 1 shown COVID-19 was most likely occurred in male group (53.70%). In the age group, more than half patients with age range between 45 and 64 years old (50.90%) were detected in COVID-19 positive.

Table 1. Demographic of COVID-19 Patients (n=214)

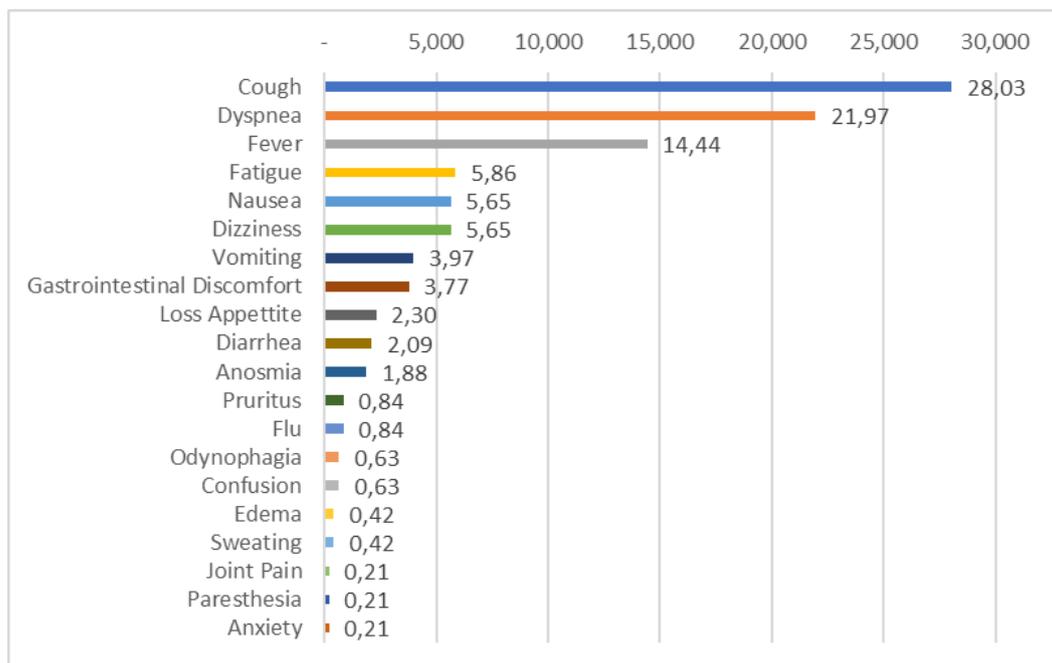| Characteristics		Frequency	%
Sex	Male	115	53.70
	Female	99	46.30
Age	18-44 years old	54	25.20
	45-64 years old	109	50.90
	65-74 years old	32	15.00
	>74 years old	19	8.90
Severity Level	Mild	21	9.80
	Moderate	172	80.40
	Severe	21	9.80
Comorbid	Yes	191	89.30
	No	23	10.70

Figure 2. Distribution of Symptoms in COVID-19 Patients in percentages (n=478)

Most of all patients in this study were classified in moderate level (80.40%) and suited to hospitalize in order to have better monitoring. Comorbidities were highly detected in the major prevalence on these patients (89.30%). Figure 1 exposed the type of comorbidities which existed in nearly all the patients in this study. Pneumonia, diabetes mellitus, and hyper-

tension were three common diseases detected in the total case of 308 comorbidities by 27.27%, 15.58%, and 14.29%, respectively. Based on Figure 2, general symptoms occurred in respiratory infection pointed cough, dyspnea, and fever ranked as three major symptoms.
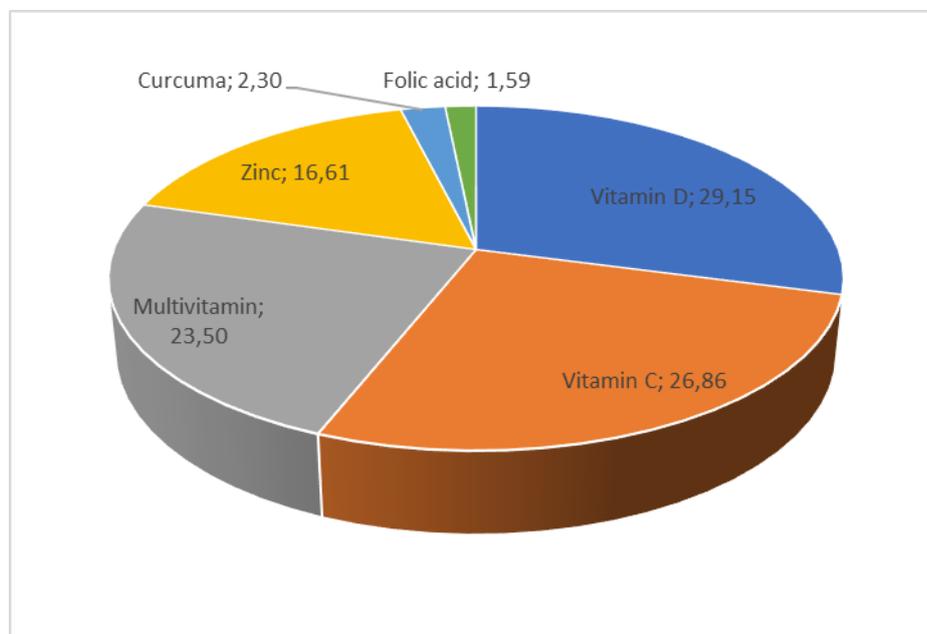

Figure 3. Prevalence of Vitamins and Multivitamins (n=566)

2. Medication Characteristics

Figure 3 placed vitamin D, vitamin C, multivitamin, zinc, curcuma, and folic acid in order according to their apply in COVID-19 patients from largest to smallest percentage.

3. Correlation between Medications and Clinical Indicator on COVID-19 Patients

The result can be seen in Table 2 and Table 3 that the use of vitamins and multivitamin only earned significant effect on those who took multivitamin as one of their therapy with 1.140 times to have chance of being recover. The utility of vitamins and multivitamin brought expectation of better outcomes in COVID-19 clinical aspects.

Table 2. Correlation Analysis between Vitamins and Multivitamin against Length of Stay

Type of Vitamins or Multivitamin		Length of Stay, n (%)		P value	OR	CI95%
		≤ 7 days	> 7 days			
Vitamin D	Yes	67 (31.30)	96 (44.90)	0.079	1.84	0.93-3.68
	No	14 (6.50)	37 (17.30)			
Vitamin C	Yes	58 (27.10)	92 (43.00)	0.706	1.12	0.61-2.06
	No	23 (10.70)	41 (19.20)			
Multivitamin	Yes	11 (5.10)	24 (11.20)	0.392	0.71	0.33-1.55
	No	70 (32.70)	109 (50.90)			

Table 3. Correlation Analysis between Vitamins and Multivitamin against Clinical Outcome

Type of Vitamins or Multivitamin		Clinical outcome, n (%)		p	OR	95% CI
		≤ 7 days	> 7 days			
Vitamin D	Yes	148 (69.20)	15 (7.00)	0.353	1.57	0.60-4.09
	No	44 (20.60)	7 (3.30)			
Vitamin C	Yes	133 (62.10)	17 (7.90)	0.437	0.66	0.23-1.88
	No	59 (27.60)	5 (2.30)			
Multivitamin	Yes	35 (16.40)	0 (0.00)	0.029	1.14	1.08-1.20
	No	157 (73.40)	22 (10.30)			

DISCUSSIONS

1. Patient's Demographics

Similar study in United States described common result as 374 out of 3,449 inpatients were male. Intrinsic biological factor was the key factor of this event where estrogen in female had several benefit effects in reducing COVID-19 exposure. Some particular mechanism of estrogen was increasing expression of antiviral and pro-inflammatory, upregulation mechanism of Angiotensin Converting Enzyme 2 (ACE2), and reducing worse outcome in COVID-19 (Eskandari et al., 2021). One research in Ecuador came up with the median age in male and female COVID-19 patients were 42 and 39, respecttively. In addition to that, age between 19-50 years old group (59.6%) reported as the most infected group which very identical with this study findings (Ortiz-Prado et al., 2021).

Many studies exhibited that the opportunity of COVID-19 infection has increased gradually with age. Degradation of T cells, B cells, and innate immune cells which led to reduction of viral clearance were convinced as the disadvantage mechanism in older people (Kang and Jung, 2020). One review analysis indicated that comorbidities made it more susceptible for patients to invade by COVID-19 infection. Those who own comorbidities had a considerable possibility to experience worse symptoms and death (Nugraha et al., 2020).

Plausible mechanism of worsening conditions in COVID-19 patients with comorbidities was robust expression of ACE-2 receptor and elevated release of proprotein convertase that allow the entry access into host cells. Comorbidities might direct to life-threatening conditions then ended up increasing of morbidity and mortality. Chronic Obstructive Pulmonary Disease (COPD), hypertension, malignancies, and HIV were commonly found among COVID-19 patients (Ejaz et al., 2020). Furthermore, a large study involved 1590 COVID-19 patients in China noted hypertension, diabetes, malignancy, and diabetes as risk factors that contribute of deteriorating factors of intensive care unit admission, ventilation, and death (Guan et al., 2020). Figure 1 showed pneumonia, diabetes, and hypertension were ranked as common comorbidities in this study. This finding was similar to the result of study previously mentioned.

Several symptoms accompanied COVID-19 patients. Cough, dyspnea,

and fever were generally occurred in most of patients. A review consisted of 24,410 adults from 9 countries (148 studies) tested positive for coronavirus captured that fever and cough were the highest prevalence symptoms by 78% and 57%, respectively (Grant et al., 2020). Convincing pathway of these symptoms explained that SARS-CoV-2 was received via respiratory and bind to the nasal epithelial cells in the upper respiratory tract later replicated and propagated itself. During this stage, immune system went down and the individuals made themselves highly infectious. Furthermore, this process then manifested fever, cough, and malaise (Parasher, 2021).

2. Medication Characteristics

Vitamins and multivitamins were widely used not only in COVID-19 patients but also in healthy people. Total number of vitamins and multivitamins of 214 COVID-19 patients in this study was 566. Vitamin D (29.15%), vitamin C (26.86%), and multivitamins (23.50%) were 3 types used in frequent times among 7 variants. Resemblant result displayed from a study placed in Jakarta with 3,576 participants where vitamin C took first place by 51.20% followed by multivitamins by 20.20%.

This data came up with reason that vitamin C would have protection effect from COVID-19. Previous studies mentioned the use of vitamin A, C, D, E, zinc, selenium, and copper would benefit in enhancing immune system and keep body from virus infection (Srimiati et al., 2020). Immunomodulatory and induces secretion of antimicrobial peptides were two claimed mechanism of vitamin D. In the other hand, stimulate Interferons (IFN) production which led lymphocyte proliferation and intensified capability of phagocytic were some certain works from vitamin C. Multivitamins gave distinct advantage through antiinflammatory and antioxidant properties that may decrease the severity of COVID-19 (Michienzi and Badowski, 2020).

3. Correlation between Medications and Clinical Indicator on COVID-19 Patients

One investigation to analyze the association between vitamin D plasma levels and COVID-19 susceptibility, severity, or hospitalization determined that no association was found from all categories (Butler-Laporte et al., 2021). The evidence of vitamin C role in COVID-19 patients was yet controversy. A rapid review stated that the use of vitamin C provided shortened period on several outcomes included Intensive Care Unit (ICU) average stay, duration of mechanical ventilation, and mortality in sepsis patients.

However, this promising impact was highly rely on the dose of vitamin C which very vary in multiple researches (Hemilä and de Man, 2021). On the contrary, one research noted that vitamin C has no correlation on COVID-19 hospitalisation or severe COVID-19 (Hui et al., 2021). A recent study performed significant reduction on oxygen support, intensive care support, or both on the apply of combination of vitamin D, magnesium, and vitamin B12 on the elderly people. This positive outcome was seemingly could made an easier way to reach recovery condition (Tan et al., 2020).

There was no association discovered between vitamin D and vitamin

C against length of stay and clinical outcome in this study whereas the only meaningful association found on the use of multivitamin to better improvement on clinical outcome marked by healed. The implycation of this study was to suggest the application of multivitamin among COVID-19 patients in order to earn better outcome.

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