

Correlation between serum vitamin D levels with severity of community acquired Pneumonia in hospitalized patients over sixty years old in Indonesia

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Abstract. *Background and aim:* Old-aged persons commonly experience vitamin D deficiency due to many factors such as insufficient vitamin D intake, multiple medications, low sun exposure, and chronic kidney disease, thus increases susceptibility to infections. Community Acquired Pneumonia (CAP) is common in old-aged persons with a high morbidity rate. Its mortality rates can even reach 50-70% if accompanied by comorbidities. This study aimed to describe the correlation between CAP severity with serum vitamin D levels in hospitalized old-aged patients. *Methods:* This is an observational study with cross-sectional design, involving 82 hospitalized old-aged patients with diagnosis of CAP. Blood samples was collected in order to measure serum Vitamin D levels. Data normality was tested with Kolmogorov-Smirnov test, while Chi Square and Mann-Whitney test was utilized for statistical analysis. Statistical significance was described as p value < 0.05. *Results:* Average serum vitamin D levels were significantly lower in severe patients than in non-severe groups ($p < 0.05$). The percentage of patients with vitamin D deficiency was also higher in the severe group compared to the non-severe group ($p < 0.05$). *Conclusions:* There is a significant correlation between serum vitamin D levels and the severity of CAP in hospitalized old-aged patients. (www.actabiomedica.it)

Key words: old-aged, vitamin D, community acquired Pneumonia

Introduction

The old-age population continues to increase every year. In Indonesia, the percentage of old-aged persons has been increased from 4.5% in 1971 to 10.7% in 2020, and it still continues to increase as in 2023, old-age population in Indonesia has reach 37,117,475 people or 13.7% of total population (1). Old-aged persons in Indonesia refers to people aged 60 years and over, both male and female (2). Old-aged persons are at a higher risk to suffer from vitamin D deficiency. Inadequate oral intake, polypharmacy, lack of sun exposure, as well as chronic kidney disease become the risk factors contribute to vitamin D deficiency in this population (2-4). Vitamin D itself is a pro-hormone

which play an important role in intestinal calcium absorption. It was firstly discovered since the emergence of ricketsia in Europe and North America in the 19th century. At the beginning, vitamin D was only known for its musculoskeletal benefits, though currently vitamin D has been widely known with its various non-musculoskeletal benefits including as therapy for malignancies, hypertension, diabetes mellitus, cardiovascular diseases, and infections (4).

Community acquired pneumonia (CAP) is the most common infectious disease among old-aged patients (2-4). The cases of CAP in old-aged persons sometimes can be challenging due to unspecific symptoms which commonly manifest as mental status disturbances, functional status alterations, and decreased

oral intake without the presence of respiratory symptoms and fever (3,5-7). Community acquired pneumonia is associated with higher morbidity and mortality in old-aged patients. The mortality rate of CAP in old-aged patients is 20%, but it can even reach 50-70% in condition with comorbidities (2-4).

Vitamin D has an important role in immunomodulation against several pulmonary infections including tuberculosis and pneumonia. Vitamin D will enhance the activity of T-helper 2 (Th2) and T-regulatory (Treg) cells while suppressing the T-helper 1 (Th1) and T-helper 17 (Th17). In addition, vitamin D activity has also been proven to be associated with lower production of C-Reactive Protein (CRP) which is an acute inflammatory protein (4-8). Based on this mechanism, vitamin D deficiency, including in old-aged persons, will impair the immune regulatory mechanism thus increase the susceptibility to infectious diseases such as CAP (2-4). Several studies have evaluated the effects of vitamin D to CAP, but the results remain inconclusive (9-16). In this study, we are describing the correlation between the levels of serum vitamin D with the severity of CAP especially in hospitalized old-aged patients.

Materials and methods

Ethical approval

This is an analytical observational study with cross-sectional design. This study was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, with a recommendation letter number: 630/UN4.6.4.5.31/ PP36/ 2023. Before enrollment to the study, all the participants were informed about the study protocol and signed a consent form. All interventions in this study were conducted under the permission of the patients.

Study population

The population of this study was old-aged patients diagnosed with CAP that hospitalized in both emergency room and inpatient installation in Wahidin

Sudirohusodo Hospital, Hasanuddin University Hospital, and Ibnu Sina Hospital in Makassar, South Sulawesi, Indonesia. This study was started in September 2023 until December 2023. The samples for this study were selected based on the inclusion and exclusion criteria. A total of 82 samples were enrolled to this study.

Inclusion and exclusion criteria

The inclusion criteria for this study were patients aged 60 years old or older, diagnosed with CAP, and have been undergone American Thoracic Society (ATS) scoring for determination of CAP severity. Patients who received vitamin D supplementation during their hospital stay were excluded.

Clinical data and sample collection

The demographic and clinical data were collected from the medical records. Blood sampling for serum vitamin D measurement was performed after the patients were diagnosed with CAP, met the eligibility criteria, and declare their willingness to be participate this study by signing the inform consent form. Blood sampling was conducted inside the hospital by collecting about 5 mL of blood from brachial vein. The blood sample were then homogenized and centrifuged. Sample analyzing was performed in the clinical pathology unit of the hospitals.

Statistical analysis

Primary outcome of our study is the correlation of serum vitamin D with the severity of CAP, while secondary outcome is the influence of several cofounding variables including gender, age, and comorbidity to the levels of serum vitamin D. Research data was analyzed by using Statistical Package for Social Science (SPSS) version 25. General characteristics of research samples was obtained by using descriptive analysis method. Data normality was assessed by using Kolmogorov-Smirnov test. Research data then was statistically analyzed with Chi-square and Mann-Witney test. Statistical significance result was described as p-value <0.05. We also classify patients

into normoalbuminemia and hypoalbuminemia with a cutoff value of 3,5 mg/dl and into normoglycemia and hyperglycemia with a cutoff value of 200 mg/dl. Patients are also classified based on their nutritional status including underweight (BMI<18.5 kg/m²), normoweight (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²), and obese (BMI≥30 kg/m²).

Results

Study population

A total of 82 of samples were included in our study, consist of 56 men (68.3%) and 26 woman (43.9%). The subjects were distributed to several groups based on their age including: 36 subjects (43.9%) in the age group of 60-65 years, 22 subjects (26.8%) in the age group of 66-70 years, and 24 subjects (29.3%) in the age group of >70 years. As many as 30 participants (36.6%) had sufficient serum vitamin D (>30-100 ng/mL), followed by 26 (31.7%) participants with insufficient serum vitamin D (21-29 ng/mL), and 26 (31.7%) participants experienced vitamin D deficiency (<20 ng/mL). According to the pneumonia severity, the participants were classified into two groups, with 52 participants (63.4%) were in non-severe group and 30 participants (36.6%) in severe group. Twenty-eight participants (34.1%) did not have comorbidity, while 40 participants (48.8%) experienced one comorbidity, and 14 participants (17.1%) have more than 2 comorbidities. The most common comorbidity found in our samples is hypertension, followed by diabetes mellitus, chronic kidney disease, malignancy, chronic obstructive pulmonary disease (COPD), and other comorbidities. Hypoalbuminemia was found in 75.6% of our samples. Majority of our participants were normoweight (67.1%) and underweight (29.3%), while only 3.6% were overweight. A total of 71 (86.6%) of patients were normoglycemia, hyperglycemia was only found in 11 (13.4%) of our samples. All of our patients received antibiotics as the therapy for their pneumonia. There are 11 (13.4%) of our patients treated with corticosteroids. Characteristics of study participants are shown in Table 1.

Table 1. Characteristics of study participants.

Variable	n	%
Gender		
Male	56	68,3
Female	26	31,7
Age (years)		
60-65	36	43,9
66-70	22	26,8
70 and above	24	29,3
CAP Severity		
Non Severe	52	63,4
Severe	30	36,6
Serum Vitamin D		
Deficiency	26	31,7
Insufficiency	26	31,7
Sufficient	30	36,6
Comorbidity		
0	28	34,1
1	40	48,8
≥2	4	17,1
Albumin (g/dL)		
Hypoalbuminemia	62	75,6
Normoalbuminemia	20	24,4
BMI		
Underweight	24	29,3
Normoweight	55	67,1
Overweight+	3	3,6
Random Blood Glucose		
Normoglycemia	71	86,6
Hyperglycemia	11	13,4
Comorbidity		
Diabetes Melitus	17	20,7
Malignancy	8	9,8
Chronic Kidney Disease	11	13,4
COPD	5	6,1
Hypertension	24	29,3
Other	5	6,1
Drugs Used		
Cephalosporin	32	39
Fluoroquinolone	33	40,2
Macrolide	16	19,5
Carbapenem Lactam	25	30,5
Vancomycin	2	2,4
Corticosteroids	11	13,4

Correlation between serum vitamin D with severity of community acquired Pneumonia

Correlation between serum vitamin D and CAP severity was analyzed using Chi-Square and Mann-Whitney test. The results showed a significant correlation between the levels of serum vitamin D and the severity of CAP ($p < 0.05$). The mean serum vitamin D was lower in subjects with severe pneumonia (22.03 ng/mL) than in subjects with non-severe pneumonia (31.86 ng/mL), p value = 0.001 (Table 2). A higher percentage of subjects with vitamin D deficiency was also reported in severe group (57.7%) compared to non-severe group (42.3%), p value = 0.014 (Table 3).

The mean of vitamin D levels was significantly lower in severe CAP (22.03 ng/mL) compared to non-severe CAP (31.66), with p value < 0.001 (Figure 1).

A significant relation between vitamin D category and CAP severity ($p < 0.05$), in which CAP severity was increased in patients with vitamin D deficiency and insufficiency compared to patients with sufficient vitamin D levels.

Table 2. Comparison of mean serum vitamin D between severe and non-severe CAP.

Severity	n	Mean Serum Vitamin D	SD	p
Non Severe	52	31,86 ng/ml	12,60	0,001
Severe	30	22,03 ng/ml	10,01	

*Mann-Whitney test

Table 3. Correlation of serum vitamin D with CAP severity.

		CAP Severity		Total
		Severe	Non-Severe	
Deficiency	n	15	11	26
	%	57,7%	42,3%	100,0%
Insufficient	n	9	17	26
	%	34,6%	65,4%	100,0%
Sufficient	n	6	24	30
	%	20,0%	80,0%	100,0%
Total	n	30	52	82
	%	36,6%	63,4%	100,0%

Chi Square test ($p = 0,014$)

Influence of other cofounding factors to severity of community acquired Pneumonia

In this study, we also evaluated the influence of several cofounding factors to the severity of CAP. The cofounding factors are gender, age, and comorbidity. Our study did not find any significant correlation ($p > 0.05$) between these cofounding factors to CAP severity (Tables 4, 5 and 6).

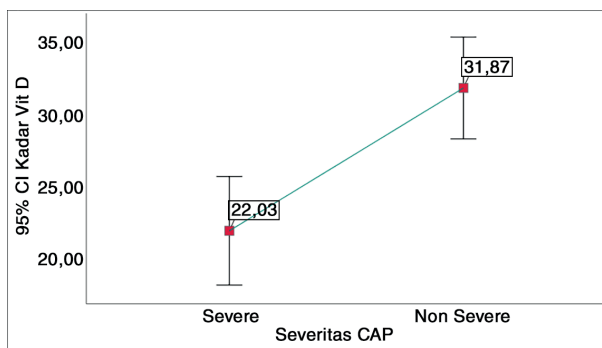


Figure 1. Mean vitamin D levels based on the CAP severity.

Table 4. Correlation of gender with CAP severity.

		CAP Severity		Total
		Severe	Non-Severe	
Male	n	20	36	56
	%	35,7%	64,3%	100,0%
Female	n	10	16	26
	%	38,5%	61,5%	100,0%
Total	n	30	52	82
	%	36,6%	63,4%	100,0%

Chi Square test ($p = 0,810$)

Table 5. Correlation of age with CAP severity.

		CAP Severity		Total
		Severe	Non-Severe	
60-65	n	13	23	36
	%	36,1%	63,9%	100,0%
66-70	n	7	15	22
	%	31,8%	68,2%	100,0%
>70	n	10	14	24
	%	41,7%	58,3%	100,0%
Total	n	30	52	82
	%	36,6%	63,4%	100,0%

Chi Square test ($p = 0,784$)

Table 6. Correlation of comorbidity with CAP severity.

		CAP Severity		Total
		Severe	Non-Severe	
Present	n	23	31	54
	%	42,6%	57,4%	100,0%
Absent	n	7	21	28
	%	25,0%	75,0%	100,0%
Total	n	30	52	82
	%	36,6%	63,4%	100,0%

Chi Square test (p=0,117)

Discussion

Effect of vitamin D to CAP has been observed in several studies, but the exact conclusion remains unclear. Many clinical studies revealed an inverse correlation between vitamin D to CAP, both the incidence and worse outcomes (9-12), but there were also study that did not find significant correlation between vitamin D to CAP (14), and some studies even find inconclusive correlation between vitamin D and CAP (15,16). Our study focusing to evaluate the correlation between vitamin D with severity of CAP, especially in hospitalized old-aged patients. In our study, the mean of serum vitamin D was found to be lower in subjects with severe CAP (29.70) compared to non-severe (48.31%). Our results showed a significant relation between low vitamin D levels with CAP severity in hospitalized old-aged patients. This result is in line with a meta-analysis by Fang Zhou Y et al (2019) which also found relation between low serum vitamin D with the risk for CAP exposure (13). Another study by Georgakopoulou Vasiliki E. et al (2020) also revealed a positive correlation between low serum vitamin D with CAP severity (17).

The explanation for the correlation between low serum vitamin D to severity of CAP can be due to antimicrobial property of vitamin D which is mediated by its activity in neutralizing endotoxins and stimulating the production of antimicrobial peptide in lymphocytes and respiratory epithelial cells. Vitamin D stimulates the production of effective antimicrobial peptide such as cathelicidin and β -defensin through the binding to its receptor in immune cells including neutrophil, monocytes, natural killer (NK) cells, and

respiratory epithelial cells (18,19). Cathelicidin is potent against both gram positive and gram negative bacteria, as well as mycobacteria in the skin, respiratory tract, and gastrointestinal tract. Patients with serum vitamin D under 20 ng/mL will fail to produce cathelicidin thus increase the risk for infections, including pneumonia (20-22).

Serum vitamin D tends to be lower in CAP patients in critical condition or with sepsis (23-26). Vitamin D is not only affecting the respiratory infections, but also influencing the severity of CAP. In a study of Laird E et al. (2022), 13% of the participants have a low serum vitamin D, with lower CRP (an acute phase inflammatory protein produced by the liver), is observed in participants with sufficient vitamin D levels (23-26). In addition, a study of Kuwahara et al (2020) also found a correlation between low vitamin D levels with incidence of respiratory infections (23-26).

The limitation of this study is the data are limited to a small group of patients.

Conclusion

In this study, we found a significant correlation between low vitamin D levels with CAP severity in hospitalized old-aged patients. Low vitamin D were more common found in patients with severe CAP. In the other hand, gender, age, and comorbidity did not have a significant correlation between CAP severity in hospitalized old-aged patients.

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