Profile of Vitamin D and Interleukin-8 in COPD Exacerbation

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Profile of Vitamin D and Interleukin-8 in COPD Exacerbation

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Abstract: Background: To determine the profile of vitamin D and interleukin-8 (IL-8) in COPD exacerbation.

Method: This research is an analytical study with a cross-sectional approach conducted at the Wahidin Sudirohusodo Hospital Makassar from March-June 2020. Serum levels of vitamin D (25-hydroxyvitamin D) and IL-8 were measured using the ELISA method in 65 exacerbated COPD patients based on clinical examination, chest radiograph, & spirometry. The exacerbation criteria were based on Anthonisen and divided into two groups according to the exacerbation frequency in the past year (frequent exacerbations was often ≥ 3 times/year, infrequent exacerbation < 3 times/year) and related to gender, age, nutritional status, smoking status based on the Brinkman index, and obstruction degree according to the Global Initiative for Obstructive Lung Disease (GOLD) 2019.

Results: This study consisted of 65 exacerbated COPD subjects (62 men, 95.4%), with age of ≥ 60 years 73.8%, frequent exacerbations of ≥ 3 times/year, 69.3%, vitamin D deficiency status of 76.9 %, and it was found to be significantly lower (15.1 ng/ml) at the frequent exacerbations of ≥ 3 times/year (P <0.01). The means of IL-8 levels were 187.48 ±68.30 ng/L and found to be significantly higher (206.7 ng/L) in the frequent exacerbations ≥ 3 times/year (P <0.01). In all subgroups according to gender, age, nutritional status, smoking status, and obstruction degree, there was a tendency for the lowest vitamin D and higher IL-8 in the frequent exacerbations of ≥3times/year.

Conclusion: Vitamin D levels were found to be the lowest and IL-8 was higher in COPD patients with frequent exacerbations of ≥ 3 times/year, compared to those with the infrequent exacerbations of < 3 times/year.

Keywords: COPD exacerbation, vitamin D, Interleukin-8

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the airways and is characterized by the release of inflammatory mediators. The current study found that the concurrent increase in serum interleukin-6 (IL-6), interleukin-8 (IL-8), TNF-α, blood eosinophils in COPD patients, especially in the acute exacerbation phase, but IL-8 is

considered to have sensitivity, which is better than other cytokines (IL-6 and TNF-α), commonly used as an indicator for COPD exacerbations (1).

COPD patients are prone to exacerbations causing a decrease in the quality of life and health status of the sufferer, whereas the causative mechanism triggering the exacerbation frequency in COPD is largely unknown (2). In recent years, research on the role of vitamin D in various diseases has received considerable attention, especially the relation of vitamin D to risk, severity, and exacerbations in COPD (3). Observational studies have found a high prevalence of vitamin D deficiency in COPD patients, with vitamin D influencing the pathogenesis and severity of COPD in several ways. Vitamin D plays a role in the immune system, influences the frequency of respiratory infections triggering acute exacerbations of COPD, plays a role in the regulation of inflammatory cytokines in the airways including IL-8. In a clinical trial conducted by Ferarri R *et.al*, it was shown that vitamin D3 supplementation in COPD patients with hypovitaminosis D could prevent exacerbations (4,5)

Although many observational studies support a strong relationship between vitamin D and the incidence of COPD exacerbations, a definite causal relationship between the two has not been proven (6). Ilyas *et.al* in their study found that vitamin D levels were not related to TNF-α on COPD severity (7).

Based on a literature study, in Indonesia, there have been no studies evaluating the profile of vitamin D and IL-8 in COPD exacerbation. Therefore, we conducted this study.

2. METHOD

2.1 Research Subjects

This research is an analytic study with a cross-sectional approach conducted at Dr. Hospital. Wahidin Sudirohusodo Makassar and network since March-June 2020. The variables assessed were COPD exacerbation based on clinical examination, chest radiograph, & spirometry. Exacerbation criteria were based on Anthonisen and divided into two groups according to exacerbation frequency in the past year (the frequent exacerbations was often ≥ 3 times/year; the infrequent exacerbations was often <3 times/year), age, sex, nutritional status, smoking status based on the Brinkman index, obstruction degree based on the criteria of the Global Initiative for Obstructive Lung Disease (GOLD) 2019, the examination of vitamin D levels, and IL-8 levels.

2.2 Inclusion and Exclusion Criteria

COPD patients are those experiencing exacerbations and willing to take part in the study and sign a letter of consent. Exclusion criteria are patients suffering from pulmonary infectious diseases and/or other obstructive diseases, heart failure, and systemic inflammation.

2.3 Data Collection

Data were collected by clinical examination, chest X-ray examination, spirometry, checking of serum vitamin D levels (25-hydroxyvitamin D), and IL-8 levels.

2.4 Diagnosis Criteria

Exacerbation of chronic obstructive pulmonary disease was defined based on Anthonisen criteria, namely increased shortness of breath, an increase in the amount of sputum,

and a change in sputum color. The exacerbation frequency was defined as the number of exacerbations experienced by patients in the past year, divided into two groups, namely infrequent exacerbations of < 3 times/year and frequent exacerbations of ≥ 3 times/year.

Measurement of vitamin D levels in the serum of research subjects was examined by the ELISA method. The results for serum levels (25-hydroxyvitamin D) are reported quantitatively (in ng/mL units). According to the Endocrine Society: Deficient is 0-20 ng/ml, Insufficient is 21-29 ng/ml, Sufficient is 30-100 ng/ml and Toxic is > 100 ng/ml. The standard curve value as stated in the manual for examining Vitamin D on ELISA is 5 - 1500 pmol/L.

Measurement of IL-8 levels in the serum of study subjects was examined by the ELISA method. The results of serum IL-8 levels are reported quantitatively (in units of pg/mL). The standard curve value as stated in the IL-8 examination manual on ELISA is 31.2 - 2000 pg/mL.

2.5 Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22. The statistical analysis carried out was descriptive statistical calculations and frequency distribution as well as Pearson's Correlation statistical tests, Independent-t, and Anova test. The result of the statistical test is significant if the p-value is <0.05.

2.8 Ethical License

This research has fulfilled the ethical license of the Biomedical Research Commission on Humans, Medical Faculty of Hasanuddin University with the number of 316/UN4.6.4.5.31/PP36/2020.

3. RESULTS

3.1 Characteristics of Research Subjects

This study involved 65 research subjects consisting of 62 males (95.4%) and 3 females (4.6%). There were 48 people aged ≥ 60 years old (73.8%) and 17 people aged < 60 years old (26.2%). Based on nutritional status, the normal ones were 38 people (58.5%), under nutrition ones were 15 people (23.1%), and over nutrition, ones were 12 people (18.4%). Smoking status based on the Brinkman Index found 31 people (47.7%) were moderate smokers, 19 people (29.2%) were heavy smokers, and 15 people (23.1%) were light smokers.

Based on GOLD spirometry, the patients with severe, moderate, very severe, and mild obstructions were 27 people (41.5%), 16 people (24.6%), and 13 people (20%), and 9 people (13.8%), respectively. Based on the exacerbation frequency, it was found that the group of frequent exacerbation was ≥ 3 times/year with 44 people (69.3%) and the group of infrequent exacerbations was <3 times/year with 21 people (30.7%). For vitamin D levels, based on the endocrine society classification, there was a deficiency of 50 people (76.9%), the sufficiency of 10 people (15.4%), insufficiency of 4 people (6.2%), and toxic of 1 person (1.5%). The mean of IL-8 concentration in exacerbated COPD was 187.4868.30 with a minimum concentration of 81.23 ng/L and a maximum concentration of 511.06 ng/L.

Table 1. Subjects 'Characteristics (n=65)			
Variables		**N**	**%**
Gender	Male	62	95.4
	Female	3	4.6
Age	<60 years old	17	26.2
	≥ 60 years old	48	73.8
Nutritional Status	Lack	15	23.1
	Normal	38	58.5
	Over	12	18.4
Smoking Status	Light	15	23.1
Brinkman Index	Moderate	31	47.7
	Heavy	19	29.2
Obstruction Degree	Light	9	13.8
Based on GOLD	Moderate	16	24.6
	Heavy	27	41.5
	Very heavy	13	20.0
Exacerbation Frequency	≥ 3 times/year	44	69.3
	< 3 times/year	21	30.7
Vitamin D	Deficiency	50	76.9
25-(OH)D	Insufficiency	4	6.2
	Sufficiency	10	15.4
	Toxic	1	1.5
Interleukin 8 Levels	187.48±68.30		

3.2. *Profile of Vitamin D Based on Exacerbation Frequency*

Table.2 Vitamin D Levels Based on Exacerbation Frequency

Variable	Exacerbation Frequency	N	Mean	SD	p
Vitamin 25-(OH) D Level	<3 times/year	21	35.9	31.3	0.007
	≥3 times/year	44	15.1	7.9	

Table 2 shows that vitamin D levels are lower (15.1) at the frequent exacerbations of ≥ 3 times/year compared to vitamin D levels (35.9) at the infrequent exacerbations of < 3 times/year and this difference was statistically significant. (P <0.01)

3.3 Profile of Vitamin D Based on Subjects' Characteristics

The profile of vitamin D on the research subjects 'characteristics is shown in Table 6. Both male's and female's vitamin D levels were lower in the frequent exacerbations of ≥3 times/year compared to infrequent exacerbations of < 3 times/year which were only in men, meaning statistically significant (p <0.05). Based on age, vitamin D levels were significantly lower in the exacerbation frequency ≥3 times/year, and in both aged ≥ 60 years and < 60 years (p < 0.05) subjects. For all nutritional status, vitamin D was lower in the exacerbation frequency ≥3 times/year, but only one normal nutrient and more were significant (p <0.01). For all smoking status based on the Brinkman index, vitamin D was lower in the exacerbations frequency ≥3 times/ year but only in moderate and heavy smokers, the vitamin D level was statistically significant (p <0.05). For the obstruction degree based on our GOLD, we combined two groups of mild and moderate and severe and very severe because the subjects were not in one group so they could not be tested and the resulted that vitamin D levels were lower in the exacerbation frequency ≥ 3 times/year both in mild//moderate obstructions or severe/very severe obstruction degree but not statistically significant (p> 0.05).

Tabel 3. Vitamin D Profile to Subjects 'Characteristics

	Exacerbation Frequency						p
	< 3 times/year			**≥ 3 times/year**			
Gender	N	Mean	SD	N	Mean	SD	
Male	19	36.1	32.6	43	15.1	8.0	0.012

Female	2	34.5	23.2	1	11.8	.	0.571
Age							
≥ 60 years old	14	25.6	17.0	34	15.5	8.9	0.010
< 60 years old	7	56.6	43.6	10	13.6	2.0	0.040
Nutritional status							
Under nutrition	5	54.2	51.3	10	19.5	14.6	0.061
Normal nutrition	12	29.0	23.8	26	14.3	4.2	0.004
Over nutrition	4	33.9	14.7	8	12.2	1.5	0.001
Smoking Status							
Light Smoker	12	37.7	34.8	5	21.6	17.4	0.347
Moderate Smoker	6	30.7	30.7	23	15.3	7.0	0.030
Heavy Smoker	3	39.3	26.5	16	12.6	2.4	0.000
Obstruction Degree							
Mild/Moderate	17	41.4	32.6	8	26.3	13.7	0.224
Severe/Very Severe	4	12.6	0.7	36	12.6	1.8	0.944

3.4. IL-8 Profile Based on Exacerbation Frequency

Table.4 IL-8 Levels Based on Exacerbation Frequency

Variable	Exacerbation Frequency	n		Mean	SD	P
IL-8	<3 times/year	21		147.2	40.2	0.001
	≥ 3 times/year	44		206.7	70.8	

In Table 4, the IL-8 levels are higher (206.7) in the frequent exacerbations of ≥ 3 times/year compared to IL-8 levels in the infrequent exacerbations of <3 times/year (147.2), and this difference was significant according to statistics (P <0.01).

3.5. IL-8ProfileBasedonSubjectsCharacteristics.

The IL-8 profile on the research subjects' characteristics can be seen in Table 8. Based on gender of, both male and female, the IL-8 levels were found to be higher at the exacerbation frequency of ≥ 3 but only in males, according to statistics ($p < 0.05$), for ages ≥ 60 and < 60 years old, the IL-8 levels were found to be higher at the exacerbation frequency of ≥ 3 times/year, but only for those aged > 60 years old were statistically significant ($p < 0.01$). Based on all nutritional status, the IL-8 levels were higher in the exacerbation frequency of ≥ 3 times/year, but only in normal nutrition and over-nutrition the IL-8 levels were statistically significant ($p < 0.05$). For all smoking status, based on the Brinkman index, the IL-8 levels were higher at the exacerbations frequency of ≥ 3 times/year, but only in light and heavy smokers, the IL-8 levels were statistically significant ($p < 0.05$). For the IL-8 profile based on the GOLD obstruction degree, we also combined two groups of light and moderate as well as severe and very severe groups because the subjects were not in one group so they could not be tested and the results obtained were higher IL-8 levels at the exacerbation frequency of ≥ 3 times compared to < 3 times in the light/moderate obstruction and severe/very severe obstruction, but this difference was not statistically significant ($p > 0.05$).

Table.5 IL-8 Profile to Subjects 'Characteristics

	Exacerbation Frequency						
	< 3 times/year			**≥ 3 times/year**			
Gender	N	Mean	SD	N	Mean	SD	p
Male	19	144.6	41.3	43	204.4	70.0	0.001
Female	2	171.4	19.7	1	306.1	.	0.113
Age							
≥ 60 years old	14	147.3	43.5	34	199.9	52.4	0.002
<60 years old	7	146.9	35.8	10	229.8	114.7	0.055
Nutritional Status							
Under Nutrition	5	149.4	48.4	10	213.6	109.4	0.238
Normal Nutrition	12	149.9	38.3	26	204.8	60.7	0.007
Over Nutrition	4	136.3	45.5	8	204.5	46.8	0.038

Smoking Status							
Light Smoker	12	133.4	42.7	5	194.3	66.4	0.038
Moderate Smoker	6	161.7	27.8	23	175.9	30.6	0.313
Heavy Smoker	3	172.9	38.0	16	254.9	88.6	0.033
Obstruction Degree							
Mild/Moderate	17	136.6	37.4	8	146.1	27.0	0.532
Severe/Very Severe	4	191.9	4.6	36	220.2	70.6	0.433

4. DISCUSSION

From this study, it was found that most subjects studied were male, namely, people (95.4%) compared to only three women (4.6%). This result is in line with the research of Raherison C, *et al*. stating that COPD affected men twice more than women (8). Data in Indonesia, based on the 2013 Basic Health Research (*RISKESDAS*), showed the prevalence of COPD was higher in men (4.2 %) compared to women (3.3%) (9).

In this study, COPD was found to be more frequent at the age of ≥ 60 years old, namely 48 people with a mean of 66.8 ±9.6 years old. Woldeamanuel, *et al*. in their study stated that the age of 50 years and over had a significant relationship with the high prevalence of COPD(10). Meanwhile, the highest number of doctor visits with COPD experiencing exacerbations reported by Donalson*et al*. in their study was at the age of 55-64 years old(11).

The study of Crim, *et al*. mentioned that one of the factors influencing the COPD exacerbations was BMI < 25. A low BMI is very susceptible to pneumonia, oxidative stress, and tissue hypoxia that can worsen COPD conditions (12). This case is in line with the results of our study where the presentation of exacerbated COPD patients with BMI < 25 was 84.6% (under and normal nutrition).

Worldwide, the most common major risk factor for COPD is smoking (13). In this study, we obtained the results where most subjects based on smoker status were moderate (47.7%) followed by heavy smoker status (29.2%) then light smokers (23.1%). This study result is not in line with the study conducted by Riesco, *et al*. finding that heavy smokers tended to experience more frequent exacerbations and worsen the quality of life in COPD patients (14).

This study found that most of the subjects had a severe degree of obstruction, namely 41.5%. This result is in line with the study of Carverley, *et al*. Their analysis found a higher proportion of exacerbations in the population with a severe degree of obstruction FEV1 < 50% compared to those with FEV1 ≥ 50% (15). In our study, the proportion of subjects with severe and very severe obstruction was found to be the highest in heavy smokers (84.2%). This case is consistent with a study by Donaldson *et al*., where the obstruction degree was

related to the patient's smoking history and the incidence of repeated exacerbations could further exacerbate FEV1 values in COPD patients (11).

In this study, we found that the most frequent exacerbations were ≥ 3 times/year, namely 44 people (69.3%) compared to 21 people (31.7%). This result is in line with the study of Suissa, *et al*. They reported that the risk of exacerbations increased threefold after the second exacerbation. In general, a history of exacerbations can increase the risk of mortality (16).

For vitamin D levels, in our study, the highest proportion of vitamin D deficiency was 76.9%. This result is in line with the study of Forli *et al*. reporting that in a small sample of patients with advanced COPD waiting for lung transplantation, the majority suffered from vitamin D deficiency (25 -OHD < 20 ng/ml) (17). Ferari*et al*. in their study said that there was a relationship between low vitamin D levels and COPD exacerbations (5).

4.1. Profile of Vitamin D Level in CPOD Exacerbations

In general, the profile of vitamin D in COPD exacerbations in this study was found to be low based on the frequent exacerbations and high at the infrequent exacerbations and this difference was statistically significant ($p < 0.01$). This result is in line with a study conducted by Malinovschi A *et al*., where they analyzed vitamin D levels in COPD patients grouped based on the exacerbation frequency in the last year. The results showed that the high prevalence of vitamin D deficiency in patients with frequent exacerbations was compared to infrequent exacerbations and the proportion of subjects with severe vitamin D deficiency was the greatest frequent exacerbations (18).

This phenomenon has been widely studied where low vitamin D levels are related to decreased immune response and an increased risk of infection, whereas COPD exacerbations are often triggered by a viral or bacterial infection. Several clinical trials have shown that supplementation reduces the risk of exacerbations in COPD patients with low vitamin D levels whereas vitamin D functions to increase innate immunity by increasing antimicrobial peptides and reducing the expression of pro-inflammatory cytokines (5,7,19). The results of this study indicated that most COPD patients were deficient in vitamin D and that severe deficiency was mainly associated with the group with frequent exacerbations and this finding was consistent after correlating age groups, nutritional status, smoking status, and obstruction degree where the tendency for deficiency was associated with the group of frequent exacerbations. In a meta-analysis study of Zhu M *et al*., the five studies analyzed showed that low levels of vitamin D in COPD were exacerbated (3).

4.2. Profile of Interleukin-8 Levels on COPD Exacerbations

The profile of IL-8 levels in this study generally showed the highest in COPD exacerbations with a frequent exacerbations of ≥3 compared to IL-8 levels in infrequent exacerbations of <3, and this difference was statistically significant ($p < 0.01$). This result is in line with a study conducted by Tumkaya M *et al*. wherein their study there was a positive correlation between the airway inflammation marker IL-8 and the frequent exacerbations in COPD (20). Another study by El-Shimy WS *et al*. found that serum IL-8 statistically increased during the exacerbation phase in COPD (21).

The IL-8 concentration obtained in this study generally increased concerning the exacerbation frequency and this result was consistent after being associated with all groups based on nutritional status, smoking status, obstruction degree wherein all groups IL-8 concentrations had a tendency to increase according to the exacerbation frequency. Moreover, in a study conducted by Chung KF, the increase in IL-8 was also significant in the sputum of COPD patients with frequent exacerbations of ≥ 3 times/year compared to those with infrequent exacerbations of < 3 times/year. (22)

5. CONCLUSION

The COPD patients with frequent exacerbations of ≥ 3 times/year had the lowest Vitamin D levels and higher IL-8 compared to the patients with infrequent exacerbations of < 3 times/year.

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Conflict of interest

We have no conflict of interest to declare.

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ORIGINALITY REPORT

%17	%12	%13	%3
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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