Nusantara Medical Science Journal
Volume 6 Issue 2, July - December 2021
P-ISSN: 2460-9757, E-ISSN: 2597-7288
Nationally Accredited Journal, Decree No. 36/E/KPT/2019.

Original Article

Correlation between Interleukin-1β serum level with severity of airway obstruction in Exacerbation Chronic obstructive pulmonary disease (COPD)

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ARTICLE INFO

Keywords:
Interleukin-1β; COPD; Exacerbation; airway obstruction;

How to cite:
Nurfajar BM., Ilyas M., Arief E., Djaharuddin I., Nurisyah S., Putrawan HA. (2021). Correlation between Interleukin-1β serum level with severity of airway obstruction in Exacerbation Chronic Obstructive Pulmonary Disease (COPD). Nusantara Medical Science Journal, 6(2), 93-102

ABSTRACT

Introduction*: To observe the relation between Interleukin-1β with exacerbation of Chronic Obstructive Pulmonary Disease (COPD).* ***Methods:*** *This study was designed for a cross-sectional study. 65 acute exacerbation COPD patients were selected. The serum level of Interleukin-1β was recorded.* ***Results:*** *Most of the subjects are men (95,4%), moderate smokers (41,5%), normal BMI (61,5%), more than 60 years old (73,8%), have more than 2 exacerbations in a year (67%), severe airway obstruction (41,5%) and mostly in group D (80%). The mean level of Interleukin-1β was 1.63 pg/ml range from 0,009-17,62 pg/ml. Kruskal Wallis analysis test noticed significant differentiation mean serum level of Interleukin-1β in several groups of GOLD. p<0,05. There was no correlation between serum level of IL-1β with the severity of airway obstruction (GOLD) p>0.05.* ***Conclusions****: there was no correlation between the severity of airway obstruction with serum level of IL-1β in acute exacerbation of COPD. there was a vicious trend of increasing IL-1β serum level according to the severity of airway obstruction mainly seen in GOLD 2, GOLD 3, and GOLD 4.*

DOI:
10.20956/nmsj.v6i2.18850

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a common preventable and treatable disease. This disease is characterized by persistent respiratory symptoms and airflow obstruction caused by damage to the airways or alveoli due to exposure to harmful particles or gases significantly influenced by host factors.[1] According to a report from the World Health Organization, an estimated 65 million people suffer from this disease. COPD is moderate to severe. More than 3 million people died from COPD in 2005.[2] COPD is also estimated to be the seventh leading cause of disability in the world.[3]

Inflammation is an important factor that causes COPD. The chronic inflammation that occurs in COPD primarily involves the infiltration of neutrophils, macrophages, lymphocytes, and other inflammatory cells into the small airways. Inflammation that lasts continuously for a long time causes permanent damage to airway structures. Thus, it becomes a major factor in the incidence of COPD.[4] Inflammation in COPD is evidenced by an increase in various pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α.[5,6,7] One of the causes of COPD exacerbations is a viral or bacterial infection.8 Interleukin-1β is one of the pro-inflammatory cytokines that play a role in the initial defense against infection.[9] In addition, it is also considered to play an important role in the pathogenesis of COPD.[10,11] IL-1β is a key role In the pathogenesis of COPD and COPD exacerbations, researchers are interested in finding the relationship between IL-1β levels and COPD exacerbations.

2. METHODS

This study was a cross-sectional design aimed at determining the relationship between IL-1β levels and severity of airway obstruction in COPD exacerbation patients. The level of IL-β was measured in patient blood serum using ELISA (Kit By Bioassay Technology Lab) with a sensitivity of 10,07pg/mL. The severity of airway obstruction was measured with a spirometry test. The spirometry result is then divided according to the GOLD 2020 classification. The population of this study was COPD exacerbation patients in DR. Wahidin Sudirohusodo general hospital and its network between January 2018-December 2020. The diagnose of COPD exacerbation is based on anamnesis, physical examination, chest X-Ray, and spirometry test. This study's inclusion criteria were COPD exacerbation patients willing to take part in the study after obtaining a brief of informed consent. Patients were excluded from the study if they had arthritis rheumatoid. The sample was recruited through the consecutive method, patients who meet the inclusion and exclusion criteria included in this study.

Statistical analysis

The research analysis in this study used SPSS version 25. Numerical data were presented as mean. Categorical data presented in frequency and percentage. Normality tes using Kolmogorov-Smirnov test. Kruskal Wallis test was used to see a statistically significant level of IL-1β between the GOLD group. Post hoc analysis was used to

evaluate the true significance between the group. Correlation test in this study measured with Pearson correlation test if the data were normal and Spearman if the data were not naturally distributed. All values were considered significant if p<0,05.

3. RESULTS

This study involved 65 subjects who met the inclusion criteria. In this study, most of the subjects are men (95.4%). The age of the subjects in this study was dominated by subjects aged ≥60 years old (73.8%) compared to the age of subjects <60 years (26.2%). Subjects were divided into 3 nutritional groups based on body mass index (BMI), most of the subjects were in the normal nutrition group 40 people (61.5%) followed by the undernutrition group 15 people (23.1%), and over nutrition as 10 people (15.4%). The smoking status of the subjects was assessed using the Brinkman index into three groups, namely light smoking status, moderate smoking status, and heavy smoking. In this study, 29 subjects (44.6%) were included in the criteria for moderate smoking. Heavy smokers were 19 subjects (29.2%) and the remaining 14 people (21.5%) were included in the criteria for light smokers.

Table 1. Characteristics of the research subjects

Characteristics of the research subjects		N (65)	%
Gender	men	62	95.4
	female	3	4.6
Severity of obstruction	Gold 1	9	13.8
	Gold 2	16	24.6
	Gold 3	27	41.5
	Gold 4	13	20.0
Severity of COPD	A	1	1.5
	B	0	0
	C	12	18.5
	D	52	80.0
Smoking status	smoker	62	95.4
	Non smoker	3	4.6
Brinkman Index	Mild	14	21.5
	Moderate	29	44.6
	Severe	19	29.2
Nutritional status	thin	15	23.1
	Normal	40	61.5
	overweight	10	15.4
Frequency of Exacerbation	1 time	5	7.7
	2 times	16	24.6
	> 2 times	44	67.7

Age	< 60 years old	17	26.2
	≥60 years old	48	73.8

Data normality test

We carried out normality data test using Kolmogorov-Smirnov test to see the normality in Interleukin-1β result. We found the result data in this study does not normally distribute because the p-value= 0.01 (p<0.05). The correlation between the level of IL-1β with the degree of airway obstruction was measured using the Spearman statistic test.

Correlation between mean level of IL-1β with severity of airway obstruction

The severity of airway obstruction was measured using the GOLD criteria which was divided into 4 groups based on the results of spirometry examination. Subjects were divided into 4 groups, GOLD 1 (mild obstruction), GOLD 2 (moderate obstruction), GOLD 3 (severe obstruction), and GOLD 4 (very severe obstruction). In this study, most of the subjects had severe obstruction with a total sample of 27 people (41.5%). Subjects with moderate obstruction amounted to 16 people (24.6%). Meanwhile, the number of subjects with very severe and mild obstruction were 13 subjects (20%) and 9 subjects (13,8%) respectively (Table 1).

Table 2. Relationship of mean IL-1β level with the frequency of exacerbation using Kruskal Wallis test

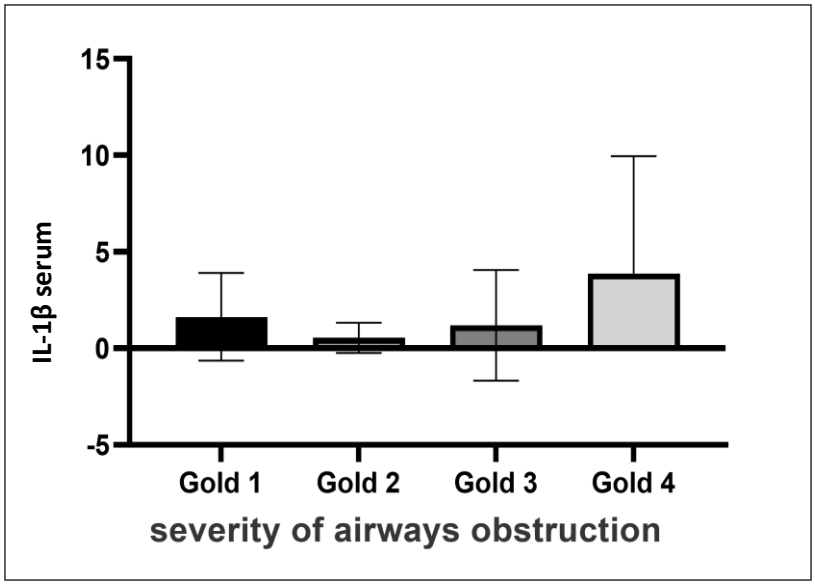
Frequency of exacerbation	Mean	SD	Median	Minimum	Maximum	P value
1	1.60	3.08	0.29	0.02	7.09	0.725**
2	0.76	0.99	0.33	0.06	2.86	
> 2	1.95	4.11	0.42	0.00	17.62	

The frequency of exacerbations is divided into 3 categories, one exacerbation in 1 year, 2 exacerbations in 1 year, and more than 2 exacerbations in 1 year. In this study, most of the subjects experienced exacerbations. Frequency of more than two exacerbations in 1 year with a total of 44 subjects (67.7%). Those who experienced exacerbations twice and once are as many as 16 subjects (24.6%) and 5 subjects (7.7%) respectively (Table 1). The average level of IL-1β in exacerbating COPD was 1.63 pg/mL with the lowest level of 0.009 pg/ml and the highest level of 17.62 pg/mL (Table 2).

Table 3. Relationship of mean IL-1β level with severity of airway obstruction using Kruskal Wallis test

severity	Mean	SD	Median	Minimum	Maximum	P value
Gold 1	1.63	2.28	0.55	0.09	7.09	0.013**
Gold 2	0.54	0.78	0.33	0.00	2.86	
Gold 3	1.19	2.86	0.27	0.01	14.05	
Gold 4	3.88	6.08	0.90	0.21	17.62	

The mean serum IL-1β level was highest in subjects who had more than two exacerbations in 1 year with a mean of 1.95 pg/mL when compared to other subjects. The other subjects who experienced exacerbations once a year had an average IL-1β level of 1.6 pg/mL and those who experienced exacerbations twice a year had an average of 1.76 pg/mL. This difference was not statistically significant with p=0.725.



Picture 1. Relationship between mean level of IL-1β with the severity of airways obstruction.

IL-1β levels were found to be highest in subjects with GOLD 4 airway obstruction with a mean of 3.88 pg/mL. The other three groups had an average of IL-1 β consecutively: GOLD 1 1.63 pg/mL, GOLD 2 0.54 pg/mL, and GOLD 3 1.19pg/mL. These results showed a significant relationship between the severity of obstruction and serum IL-1β levels with $p<0.05$. We then performed the POST HOC test and found that the difference in levels of IL-1β to the severity of airways obstruction was statistically significant ($p<0.05$) in GOLD 2 vs. GOLD 4 and GOLD 3 vs GOLD 4. We then performed a Spearman correlation test to analyze the correlation between the mean level of IL-1β with the severity of airway obstruction in COPD patients. We found that there was no correlation between them $p>0.05$. (table.4)

Table 4. Spearman correlation test between Level of IL-1β with the severity of airway obstruction

		The Severity of airway obstruction (GOLD)
Serum level of IL-1β	r	0.167
	p	0.183
	n	65

4. DISCUSSIONS

The incidence of COPD in men and females shows different results in several countries according to the survey method, diagnostic criteria, and analytical approach used. It should be noted that almost all studies make the diagnosis of COPD based on spirometry results alone without looking at the patient's symptoms.[1] In this study, the number of male subjects was more than female. Male subjects amounted to 62 people (95.4%) while female subjects amounted to 3 people (4.6%). These results are similar to the findings of Mizarti et al in M. Djamil Hospital Padang in 2019 (83.17% male).[12] Similar results were also found by several other researchers, such as Tsai et al in 2012 in Taiwan and Hye young Kwon et al in South Korea in 2016.[13,14] The opposite result was found in Lexington, America.[15]

Until now, most data show COPD is more common in men than women. However, now there is a new pattern where the proportions of men and women are starting to be equal. This is due to the increasing number of smokers among women. This has happened in the United States since World War II. This can be seen in the NHANES III study. It appears that the prevalence of smoking among women continues to increase.[1]

This study divides the subjects by using the age limit of 60 years. Subjects aged more than 60 years were categorized as elderly.[16] In this study, more subjects aged over 60 years. The population of subjects aged ≥60 years was 48 subjects with a mean age of 66.8 ± 9.6 years. These findings are similar to those of the general population studies in 1990 and 2004 where the prevalence of COPD increases with age. The increased risk of COPD increases 5 times in those aged over 65 years compared to those aged 40 years.[17]

Age is an important factor in COPD. The emergence of COPD does not occur in a short time. Years of exposure to cigarette smoke and harmful gases cause changes in the structure and function of the airways. These structural and functional changes are permanent. This is what causes airway obstruction in COPD. Therefore, the higher the age of the patient, the greater the chance of suffering from COPD.[18] This is supported by the report of Donaldson et al. he reported that most COPD patients who visit health care facilities are aged 55-64 years.[19]

COPD is a chronic inflammatory disease. The increase in pro-inflammatory cytokines in COPD patients suggests this statement. Systemic inflammation that occurs in COPD causes other abnormalities such as changes in body composition and skeletal muscle.[20] Chronic inflammation that occurs in COPD patients causes them to tend to

experience cachexia. a state where they become very thin. This situation will make them susceptible to infection which in turn will cause COPD exacerbation and exacerbate pre-existing diseases. Crim et al stated that BMI <25 is a risk factor for COPD. Low BMI in COPD patients causes patients to be more susceptible to pneumonia.[21] This is following our study, where most of the subjects had a BMI <25 of 84.6% (undernutrition and normal nutrition).

Smoking behavior is a major risk factor for the incidence of COPD.[1] so smokers are more prone to suffer from COPD. In this study, it was found that most of the subjects were moderate smokers (44.6%) followed by heavy and light smokers 29.2% and 21.5%, respectively. Smoking behavior is one of the risk factors for exacerbation of COPD. This is consistent with our findings where heavy and moderate smokers are the 2 most common groups in the population of exacerbating COPD patients.

One of the risk factors for exacerbation of COPD is the severity of airway obstruction. Garcia et al reported that the higher the airway obstruction, the higher the patient mortality.[22] The ECLIPSE study provides a similar picture. This study noted that patients with severe airway obstruction had a higher visit rate when compared to those with milder ones.[23] In this study, most of the subjects were in severe obstructive condition (41.5%). This is in line with previous research.

The frequency of exacerbations was defined as the number of exacerbations experienced by the patient in the past year. In this study, we divided it into three. One exacerbation, 2 exacerbations, and more than 2 exacerbations in one year. We found that the population of subjects with more than 2 exacerbations was the largest in this study (67.7%). This is similar to the findings of Suissa et al. She reported that the risk of exacerbation increased threefold after the second exacerbation.[24]

Various kinds of pro-inflammatory cytokines are believed to play a role in the occurrence of COPD such as IL-6 and TNF-α.20 IL-1β is one of the potent pro-inflammatory cytokines.[9] It plays a role in innate and adaptive body defense.[25] Lappalainen et al conducted experiments on mice transgenic. He found that mice with overexpression of IL-1β gave an emphysematous lung picture that closely resembled the lung pictured in COPD.

There is no normal value that is used as a reference for IL-1β levels in normal people, but there have been several studies measuring IL-1β levels in normal populations. Mahajan et al found IL-1β levels in the normal population 2.15±0.26 pg/mL with a range of 0.87-2.98 pg/mL.[27] Singh et al reported IL-1β levels 2.11±0.16 pg/mL in the normal population. with a range of 0.39-2.97 pg/mL.[28] In our study the average level of IL-1β was 1.63 pg/mL with a range of 0.009-17.62 pg/mL. This value is not much different from the value in normal subjects from the 2 previous studies. We conclude that the mean levels of IL-1β in COPD patients are not much different from normal subjects. The results of this study are not the same as the research conducted by Singh et al. He found that the mean IL-1β levels of subjects with COPD were significantly higher than normal subjects with a mean of 3.14±0.07 pg/mL with a range of 2.8-4.59 pg/mL .[28] Contrast to Singh study, our finding suggests than the mean IL-1β Level in COPD patient are 1,63 pg/mL with a range 0,009-17,62 pg/mL.

The results of this study are supported by research by Amer and Sapey.[29,30] Sapey et al reported that there was no significant difference in serum IL-1β levels between healthy subjects and those with COPD. However, he found that the expression of cytokine antagonists against IL-1β (IL-1RA and IL-1R2) was significantly decreased. He considers the decrease in the antagonistic effect on the pro-inflammatory action of IL-1β causing inflammation which ultimately ends up as COPD.30 Sapey's opinion about the low expression of IL-1RA and IL-1R2 in COPD patients is supported by Oudijk's findings.[31] In this study, IL-1β levels did not show a statistically significant relationship with the frequency of COPD exacerbations and severity based on exacerbation history and CAT/mMRS scores. We have not found a similar study for comparison.

IL-1β levels in our study were found elevated in patients with severe and very severe airway obstruction (GOLD 3 and 4). This is consistent with a study conducted by Zou et al.[32] Hammand et al. found that IL-1β levels in very severe COPD were statistically higher than subjects with severe and moderate COPD. Although in this study the mean level of IL-1β was not much different from the mean value in normal subjects in other studies, if we compare the average level based on the severity of airway obstruction, we can see that the group of subjects with more severe airway obstruction has an average level of higher IL-1β.[33] This means that in the group with greater airway obstruction, inflammation is higher so that it is more at risk for exacerbations.

Our study did not find a correlation between serum level of IL-1β with the severity of airway obstruction according to the Spearman correlation statistic test ($p>0.05$). Even though there was no significant correlation statistically, there was a vicious trend of increasing IL-1β serum level according to the severity of airway obstruction mainly seen in GOLD 2, GOLD 3, and GOLD 4. As priorly mentioned, Inflammation played a significant role in COPD. Various cytokines released related to inflammation caused airway obstruction and remodeling in COPD. This might be the reason why IL-1β in COPD significantly increased in GOLD 4 patients if we compared it to GOLD 2 and GOLD 3.

5. CONCLUSION

This study suggested there was no correlation between serum level of IL-1β with the severity of airway obstruction with $p>0.05$. We also found that there was a significant differentiation mean level of IL-1β between the group of GOLD ($P<0.05$), GOLD 2 vs GOLD 3, and GOLD 3 vs GOLD 4. Even though there was no significant correlation statistically, there was a vicious trend of increasing IL-1β serum level according to the severity of airway obstruction mainly seen in GOLD 2, GOLD 3, and GOLD 4.

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.