Correlation Of Tumor Necrosis Factor Alpha Levels And Nutritional Status On The Severity Of Chronic Obstructive Lung Disease

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KEYWORDS

COPD, TNF-α, nutritional status, disease severity, inflammation

ABSTRACT:

Background: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide, characterized by persistent airflow limitation and an enhanced inflammatory response. Tumor Necrosis Factor Alpha (TNF-α) has been implicated in the pathophysiology of COPD. Additionally, nutritional status plays a critical role in disease progression and severity.

Purpose: This study aims to determine the relationship between serum TNF-α levels and nutritional status, with the severity of chronic obstructive pulmonary disease (COPD).

Methods: This study is an observational analytical study design with a cross-sectional design to assess the relationship between TNF-α and nutritional status with the severity of chronic obstructive pulmonary disease (COPD). This study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar and its Network. This study was conducted during the study period from July to September 2024

Results: Based on nutritional status, 63.6% were included in the normal, overweight and obese categories, while 36.4% were in the underweight category. In terms of obstruction severity, the sample was divided into mild-moderate (31.8%) and severe (68.2%) categories. Regarding the severity, 63.6% were in the exacerbation stage (B and E), and 36.4% were in non-exacerbation (A). For the TNF-α parameter, there were two almost balanced groups, namely < 15.49 pg/mL (52.3%) and ≥ 15.49 pg/mL (47.7%).

Conclusion: Elevated TNF-α levels and poor nutritional status are strongly associated with increased COPD severity. These findings highlight the potential of TNF-α as a biomarker and the importance of nutritional interventions in managing COPD.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of morbidity and mortality in the world. This disease is characterized by persistent respiratory symptoms and obstruction of airflow. This condition is generally caused by abnormalities in the airways and/or alveoli that interfere with overall respiratory function. This disease is associated with structural changes in the lungs due to chronic inflammation by chronic exposure to harmful particles and gases, especially cigarette smoke [1]. Chronic inflammation causes narrowing of the airways and decreased lung elasticity. This disease is characterized by symptoms of coughing, shortness of breath and sputum production [2].

According to the Global Burden of Disease (GBD) study, COPD has continued to increase to become the eighth to fifth leading cause of global disease. There were around 251 million cases of COPD. The prevalence in Indonesia is estimated at 3.7% [3]. This disease mainly occurs in patients who smoke and are over 40 years old. In 2015, the prevalence of COPD was 174 million with a death toll of 3.2 million globally.3 In Indonesia, based on basic health research data in 2013, the prevalence of COPD reached 3.7% or around 9.2 million people. Health Research from the Ministry of Health shows that the number of smokers in Indonesia is still very high, approximately 33.8% or 1 in 3 people in Indonesia smoke. Male smokers have a large proportion of around 63% [4].

Chronic obstructive pulmonary disease is associated with chronic inflammation, mainly affecting the lung parenchyma and peripheral airways and causing most of the irreversible and progressive airflow

limitation [5]. This inflammation is characterized by an increase in the number of alveolar macrophages, neutrophils, and T lymphocytes recruited from the circulatory system. Oxidative stress plays an important role in driving this inflammation. Inflammation in the lungs can promote the development and growth of lung cancer and can occur peripheral inflammation that spreads to the circulation, resulting in systemic inflammation with the same inflammatory proteins [6].

Various cytokines play an important role in inflammatory diseases of the airways, including COPD[7]. These cytokines contribute through the mechanisms of recruitment, activation, and maintenance of the survival of inflammatory cells that directly affect the inflammatory process in the airways [8]. This is evidenced by the increase in the concentration of Tumor Necrosis Factor alpha (TNF-α) based on sputum induction examination and lung biopsies of COPD patients. TNF-α is the most widely studied cytokine in COPD patients, and is a strong activator of NF-κβ and enhances the inflammatory response. TNF-α plays an important role in many inflammatory diseases that affect the lungs, such as chronic bronchitis [9].

Chronic inflammation associated with COPD not only affects the airways, but also extends to other organs in the body. This condition can trigger various comorbidities that worsen the quality of life of sufferers. One of the most common impacts is nutritional disorders, where the body has difficulty meeting nutritional needs due to ongoing inflammatory processes [10]. The role of nutritional status in the severity of COPD has become a focus of research that is increasingly receiving attention in efforts to improve the quality of life and prognosis of patients. Previous studies have shown that poor nutritional status can worsen COPD symptoms, increase the risk of exacerbations, accelerate the decline in lung function, and contribute to high morbidity and mortality rates in COPD patients [11]. Pulmonary inflammation contributes to weight loss either directly through inflammatory mediators or through catabolic intermediary metabolism. Supporting this possibility is the presence of various inflammatory mediators in airway secretions and inflammatory cell infiltration. A causal relationship between inflammatory status and weight maintenance in COPD is still unproven, although TNF-α has been implicated as a factor in weight loss [12]. Increased TNF-α and decreased nutritional status may reinforce each other's negative effects in COPD, exacerbating systemic inflammation, increasing respiratory and skeletal muscle weakness, reducing exercise capacity, and increasing the risk of infections and exacerbations [13]. This combination is associated with a worse prognosis and increased mortality. In patients with COPD admitted to a tertiary care hospital, the prevalence of malnutrition was 26% among the study population using BMI and low Forced Expiratory Volume in the first second (FEV1) values indicating decreased lung function in patients with malnutrition [14]. Statistically significant correlations between FEV1 and nutritional parameters based on body weight, Mini Nutritional Assessment (MNA) scale, BMI score, and Mid Arm Circumference (MUAC) suggest that nutritional deterioration may worsen lung function [15].

Degree of airway obstruction and severity of COPD. Low vitamin D levels are negatively associated with the degree of airway obstruction and severity of COPD. Vitamin D3 levels are negatively associated with serum TNF-α concentrations and the degree of airway obstruction and severity of COPD [16]. TNF-α plays an important role in the pathogenesis of COPD, contributing to systemic and local inflammation, elevated TNF-α correlates with disease severity and may contribute to extrapulmonary symptoms of COPD, including cachexia. Malnutrition occurs in patients with COPD and is associated with poor prognosis. Inflammatory cytokines, including TNF-α, contribute to malnutrition through increased energy expenditure and decreased food intake [17].

2. Objectives

This study aims to investigate the correlation between serum TNF-α levels and nutritional status with the severity of chronic obstructive pulmonary disease (COPD). By analyzing these relationships, the research seeks to provide a deeper understanding of the potential role of TNF-α as an inflammatory marker and the impact of nutritional status on disease progression. The findings may contribute to improved clinical management and prognostic evaluation of COPD patients.

3. Methods

This study is an observational analytical study design with a cross-sectional design to assess the relationship between TNF-α and nutritional status with the severity of chronic obstructive pulmonary disease (COPD) at Dr. Wahidin Sudirohusodo Hospital Makassar and its Network. This study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar and its Network. This study was conducted during the study period from July to September 2024. The population of this study were all patients diagnosed with chronic obstructive pulmonary disease (COPD) at the Dr. Wahidin Sudirohusodo Hospital polyclinic Makassar and its Network. The research subjects were the research population that met the criteria for stable COPD. The sampling technique used the consecutive sampling technique to meet the minimum number of samples that met the inclusion and exclusion criteria.

4. Results

Sample characteristics consist of variables of gender, age, smoking history, nutritional status, severity of obstruction, severity and TNF-α levels (**Table 1.)** which will be analyzed further. Of the total sample, the majority were male (86.4%) and a small portion were female (13.6%). Most participants were elderly (≥ 60 years) with a percentage of 72.7%, while adults (18-59 years) were only 27.3%. Most of the samples were active smokers (78.4%), while passive smokers and non-smokers were only 14.8% and 6.8%, respectively. Based on nutritional status, 63.6% were included in the normal, overweight and obese categories, while 36.4% were in the underweight category. In terms of obstruction severity, the sample was divided into mild-moderate (31.8%) and severe (68.2%) categories. Regarding the severity, 63.6% were in the exacerbation stage (B and E), and 36.4% were in non-exacerbation (A). For the TNF-α parameter, there were two almost balanced groups, namely < 15.49 pg/mL (52.3%) and ≥ 15.49 pg/mL (47.7%). The characteristics of the study sample tend to be that most of the samples are elderly, male, and active smokers who can provide an overview of the target group in this study. Most samples have normal to obese nutritional status, and many are in the severe obstruction severity category.

Table 1. Characteristics of the research sample

Variable		n	%
Gender	Male	76	86,4
	Female	12	13,6
Age	Adult (18 – 59)	24	27,3
	Elderly (≥ 60)	64	72,7
Smoking History	Non-smoker	6	6,8
Nutritional Status	Passive smoker	13	14,8
(kg/m2)	Active smoker	69	78,4
	Underweight	32	36,4
Severity of	Normal, overweight, and obesity	56	63,6
Obstruction			
	Mild-moderate	28	31,8
	Severe	60	68,2
Gender	Non-exacerbation (A)	32	36,4
	Exacerbation (B and E)	56	63,6
TNF-α (pg/mL)	< 15,49	46	52,3
	≥ 15,49	42	47,7

In the TNF-α variable, the proportion of samples with TNF-α <15.49 was higher in the elderly (71.4%) compared to adults (28.6%). For TNF-α ≥15.49, the elderly also dominated with 73.9%. Nutritional status showed that samples with less nutrition were more in the elderly (78.1%) compared to adults (21.9%). In the normal, overweight, and obesity nutrition categories, the elderly

also dominated (69.6%). The severity of obstruction in the mild-moderate category was lower (32.7%) than in the severe category (67.5%), with the elderly still dominating in both categories. The degree of severity in the exacerbation group (B and E) was higher (68.7%) compared to the non-exacerbation group (31.3%), especially in the elderly samples (**Table 2.).** Elderly people showed a higher tendency in the category of TNF-α ≥15.49, poor nutritional status, severe obstruction severity, and exacerbation. This may indicate a pattern of increased risk in the elderly group, although it was not statistically significant (p<0.05).

Table 2. Relationship between age and TNF-α, nutritional status, severity of obstruction and severity of COPD

Variable			Age		Total	p
			Adult	Elderly		
TNF – (pg/mL)	α<15,49	n	12	34	46	0,794*
		%	28,6	71,4	100	
	≥15,49	n	12	30	42	
		%	26,1	73,9	100	
Status Nutrition	Less	n	7	25	32	0,390*
		%	21,9	78,1	100	
	Normal, More, and Obesity	n	17	39	56	
		%	30,6	59,4	100	
Severity Obstruktion	Light- Medium	n	11	37	48	0,315*
		%	22,9	77,1	100	
	Weight	n	13	27	40	
		%	32,5	67,5	100	
Degree of Severity	Non Eksaserbation (A)	N	10	22	32	0,527*
		%	31,3	68,7	100	
	Eksaserbation (Bn dan E)	n	14	42	56	
		%	25	75	100	

Note : *Chi-square

Based on gender, most men had TNF-α <15.49 (89.1%), while only 10.9% of women were in this group. For TNF-α ≥15.49, men also dominated (83.3%) compared to women (16.7%). In the undernutrition category, men dominated (84.4%), while women were only 15.7%. Likewise in the normal, overnutrition, and obesity categories, men had a higher proportion (87.5%). The severity of obstruction in the mild-moderate category, men had a proportion of 85.4% and women 14.6%. For the severe category, men still dominated with 87.5%. The severity of COPD in the exacerbation category (B and E), men dominated with 89.2%, while women were only 10.8% (**Table 3**). The number of men showed a higher tendency in the category of TNF-α ≥15.49, poor nutritional status, severe obstruction severity, and exacerbation. This indicates a tendency for men to be more susceptible to worse health conditions in the context of the variables analyzed. Although there is no statistical significance (p>0.05).

Table 3. Relationship between gender and TNF-α, nutritional status, severity of obstruction and severity of COPD

Variabel			Gender		Total	p
			Man	Woman		
TNF - α	<15,49	n	41	5	46	0,429*
		%	89,1	10,9	100	
	≥15,49	n	35	7	42	
		%	83,3	16,7	100	
Status Nutrition	Less	n	27	5	32	0,681*
		%	84,3	15,7	100	
	Normal, More and Obesity	n	49	7	56	
		%	87,5	12,5	100	
Severity Obstruktion	Light-Medium	n	41	7	48	0,777*
		%	85,4	14,6	100	
	Weight	n	35	5	40	
		%	87,5	12,5	100	
Degree Severity	ofNon Eksaserbation (A)	N	26	6	32	0,291*
		%	81,2	18,8	100	
	Eksaserbation (B dan E)	n	50	6	56	
		%	89,2	10,8	100	

Note : *Chi-square

Based on smoking history with TNF-α, nutritional status, severity of obstruction, most active smokers have TNF-α <15.49 (86.1%) compared to passive smokers (8.6%) and non-smokers (4.3%). In the category of TNF-α ≥15.49, active smokers also dominate (69.1%), followed by passive smokers (21.4%) and non-smokers (9.5%). In the category of poor nutritional status, active smokers dominate (78.1%), while passive smokers and non-smokers are only 15.6% and 6.3%, respectively. In the normal, overweight, and obese categories, active smokers also dominate (77.5%). The severity of obstruction in the mild-moderate category, the proportion of active smokers is 85.4%, while passive smokers are 8.3% and non-smokers are 6.3%. For the severe category, active smokers still dominate with 72.5%. The severity of the exacerbation grade (B and E), active smokers dominate (85.7%), while passive smokers are 10.7% and non-smokers are only 3.6% (**Table 4**).

Table 4. Relationship between Smoking History and TNF-α, Nutritional Status, severity of obstruction and severity of COPD

Variable			Smoking History			Total	p
			Non Smoker	Pasif Smoker	Active Smoker		
TNF - α	<15,49	n	2	4	40	46	0,124*
		%	4,3	8,6	86,1	100	
	≥15,49	n	4	9	29	42	
		%	9,5	21,4	69,1	100	
Status Nutrition	Less	n	2	5	25	32	0,976*
		%	6,3	15,6	78,1	100	
	Normal, More dan Obesity	n	4	8	44	41	
		%	9,8	19,5	70,7	100	

Severity Obstruktion	Light-Medium	%	4	4	40	48	0,162*
		n	8,3	8,3	83,4		
	Weight	%	2	9	29	40	
		n	5,0	22,5	72,5		
Degree of Severity	Non Eksaserbation (A)	%	4	7	21	32	0,076*
		%	12,5	21,9	65,6	100	
	Eksaserbation (B dan E)	n	2	6	48	56	
		%	3,6	10,7	85,7	100	

Note : *Chi-square

Active smokers dominate all categories of variables, both in TNF-α values, nutritional status, severity of obstruction, and severity. This suggests that active smokers may have a higher risk in these categories than passive smokers or non-smokers. Although statistically, there were no significant results in the variables tested (p>0.05). In the mild-moderate obstruction severity category, most samples were in the exacerbation category (56.2%), while 43.8% were in the non-exacerbation category. In the severe obstruction severity category, the majority of samples were in the exacerbation category (72.5%), and only 27.5% were in the non-exacerbation category (**Table 5**).

Table 5. Relationship of COPD Severity (ABE) using Clinical Parameters with Obstruction Severity (GOLD)

Variable			**Degree of Severity**		**Total**	**p**
			Non Eksasebation	Eksaserbation		
Severity Obstruktion	Light-Medium	n	21	27	48	0,115*
		%	43,8	56,2	100	
	Weight	n	11	29	40	
		%	27,5	72,5	100	

*chi-square

In both categories of obstruction severity (mild-moderate and severe), the exacerbation group was more dominant than non-exacerbation, indicating that exacerbations were more common in all levels of obstruction severity. Although not statistically significant (p>0.05), there was a tendency that in the more severe categories of obstruction severity, the proportion of exacerbations was higher than in the mild-moderate category.

Table 6. Relationship between Nutritional Status and TNF-α to Severity Level

Status Nutrition	**TNF-α**		**Degree of Severity**		**Total**	**P**
			Non Eksaserbation	**Eksaserbation**		
Malnutrition	<15,49	n	2	12	14	0,854*
		%	14,3	85,7	100	
	≥15,49	n	3	15	18	
		%	16,7	83,3	100	
Normal, More, dan Obesity	<15,49	n	18	14	32	0,165*
		%	56,3	43,8	100	
	≥15,49	n	9	15	24	
		%	37,5	62,5	100	

*chi-square

Undernourished individuals were more likely to experience exacerbations, both at low and high TNF-α levels (**Table 6**). This suggests that in the undernourished group, TNF-α may be less relevant in differentiating severity. In contrast, in the normal to obese nutritional status group, TNF-α levels appeared to be more relevant in differentiating severity, with high TNF-α levels tending to be associated with exacerbations. The p-value for the undernourished group was 0.854 and the p-value for the normal, overweight and obese nutritional status groups was 0.165, indicating that the difference between TNF-α levels and severity in these groups was not statistically significant ($p > 0.05$). Individuals with malnutrition were more likely to have exacerbations, regardless of TNF-α levels. This suggests that nutritional factors may play a more dominant role in influencing severity in this group than TNF-α levels. In individuals with normal to obese nutritional status, there was a trend that higher TNF-α levels may be associated with exacerbations, although this was not statistically significant.

5. Discussion

The characteristics of the sample in this study showed that the majority of respondents were male (86.4%) with age ≥ 60 years (72.7%), most of whom were active smokers (78.4%). This proportion illustrates a high-risk group for Chronic Obstructive Pulmonary Disease (COPD). The nutritional status of the sample showed that 63.6% were in the normal to obese category, but 36.4% had poor nutritional status, indicating malnutrition in some of the population. Elderly people with a history of smoking and poor nutritional status have a higher risk of COPD severity, which found that age, gender, and smoking habits affect the progression of COPD through chronic inflammation mechanisms [18].

The results showed that high TNF-α levels (≥15.49 pg/mL) were more common in the elderly (73.9%) than adults (26.1%), and the majority of active smokers dominated all severity categories ($p>0.05$) [19]. Although not significant, immunologically elderly individuals (≥60 years) tend to experience a process known as "immunosenescence," which is a decline in adaptive immune function along with increased systemic inflammation called "inflamm-aging." This process involves an increase in proinflammatory cytokines, including TNF-α, IL-6, and CRP that contribute to the susceptibility of the elderly to chronic inflammatory diseases such as COPD. The accumulation of cellular damage due to age exacerbates the inflammatory response and decreases the body's ability to control inflammation, thereby worsening diseases such as COPD [20].

In terms of gender, men tend to have higher levels of TNF-α than women, which may be due to hormonal influences. The hormone estrogen in women has a protective effect on inflammation through modulating the activity of immune cells, such as macrophages and T lymphocytes. Conversely, in men, the lack of this hormonal modulation leads to a stronger inflammatory response, including increased levels of TNF.

This study found that patients with severe obstruction severity were more likely to be in the exacerbation group (72.5%), compared to the mild-moderate category (56.2%), with a statistically insignificant relationship ($p>0.05$). These results reflect the complexity of the relationship between exacerbation and obstruction severity, as emphasized in the GOLD criteria linking exacerbation to increased inflammation and airway damage. Exacerbations are more common in patients with severe COPD, with the main mechanisms including decreased lung function and systemic vulnerability.

This study showed that TNF-α levels were higher in the severe obstruction severity group (21.32±8.11 pg/mL) compared to the mild-moderate group (12.38±4.28 pg/mL), with statistical significance ($p<0.001$). Serum TNF-α levels in COPD patients were significantly higher than those in controls, with an average of 8.0 ± 10.1 pg/mL in COPD patients compared to 3.3 ± 0.42 pg/mL in controls. This supports the role of TNF-α as an inflammatory biomarker reflecting the degree of lung tissue damage. This study found a TNF-α cut-off value of 15.49 pg/mL through ROC analysis, with an AUC of 0.834, a sensitivity of 77.5%, and a specificity of 77.1%.20 This value indicates that TNF-α is a good enough parameter to distinguish between mild-moderate and severe obstruction severity in

COPD. The strong statistical significance of obstruction severity supports the use of TNF-α as a biomarker in risk stratification, but it is not sufficient as a single predictor for the degree of clinical exacerbation [21].

The results showed that individuals with poor nutritional status and high TNF-α levels (≥15.49 pg/mL) tended to have more severe obstruction severity (77.8%), compared to the normal nutritional group with low TNF-α levels (93.8% in mild-moderate). This relationship was statistically significant in the normal to obese nutritional group ($p<0.001$), but not significant in the malnourished group ($p=0.101$) [22]. In the normal to obese nutritional group, the body's ability to produce a more controlled inflammatory response may cause a significant relationship between TNF-α levels and obstruction severity. This reflects that inflammation plays a role in determining severity. Meanwhile, in the malnourished group, a compromised immune response may make this relationship less visible. Other factors such as respiratory muscle atrophy, protein deficiency, or inability to maintain lung tissue regeneration may also be more dominant factors than TNF-α in determining obstruction severity [23].

This study has several limitations that may affect the results of the statistical analysis. The relatively small sample size may be a major factor limiting the power of statistical tests, with many relationships between variables failing to reach statistical significance despite a visible trend. In addition, sample heterogeneity, including variations in COPD severity and differences in nutritional status, may add bias to the interpretation of results [24]. The use of a single TNF-α measurement also limits the ability to evaluate fluctuations in levels of this cytokine in acute or chronic conditions [25]. In addition, the cross-sectional study design only allows for observation of relationships between variables at a single point in time, and therefore cannot elucidate causal relationships in depth. Therefore, further studies with larger sample sizes and longitudinal or cohort designs are needed to confirm these findings and explore causal relationships in more depth.

6. Conclusion

The majority of the samples in this study were elderly men with a history of active smoking, indicating a population at high risk for COPD severity. High TNF-α levels were more common in the group with severe obstruction severity compared to mild-moderate, supporting its role as an inflammatory biomarker. The TNF-α cut-off value of 15.49 pg/mL showed a fairly good predictive ability to distinguish the severity of COPD obstruction. Poor nutritional status had a significant association with severe obstruction severity, indicating the importance of nutritional intervention in COPD management. The association between TNF-α levels and clinical severity (exacerbation) was not significant, indicating the need for further research to explore the mechanisms of COPD exacerbation. Study limitations, such as small sample size and cross-sectional design, limit generalization and assessment of causal relationships.

7. Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this literature review. No financial, institutional, or personal relationships influenced the research, analysis, or conclusions presented in this manuscript.

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