Relationship between IL-6, IL-1β, and vitamin D on frailty status in elderly women

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ABSTRACT

Background: The aging process is associated with an increase in proinflammatory markers' serum levels, indicating that a chronic inflammatory process is correlated with an increase in disability, mortality, and frailty. Pro-inflammatory cytokines that increase with the incidence of frailty syndrome are IL-6, IL-1β and TNF-α. 25-hydroxyvitamin D (25 (OH) D) deficiency is also a potential risk factor for frailty, especially in the elderly. Vitamin D deficiency is associated with a risk of falling, which can speed up the frailty process. The aim of the study is to determine the relationship between IL-6, IL-1β and Vitamin D on frailty status in elderly women in elderly integrated health services (*posyandu lansia*), Semarang City.

Methods: This study used a cross sectional design with a consecutive sampling method of 27 subjects. Subjects measured vital signs, weight and height measurements. The study subjects were then taken venous blood to measure the levels of IL-6, IL-1β and vitamin D in blood serum and assessed their frailty status. Data analysis using SPSS 25 with Spearman correlation test.

Results: There were 27 elderly women who followed this study with an average age of 67.93 years. There are 16 people with pre-frail status and 3 people with frail status. There is a significant relationship between vitamin D levels in serum and frailty status ($p = 0.008$; $r = 0.497$). Variables IL-6 ($p=0.328$) and IL-1β ($p=0.095$) had no significant relationship with frailty status.

Conclusion: Most of the elderly women have a pre-frailty status, namely as much as 59.3%. Vitamin D levels in the body have a significant and unidirectional relationship with frailty status in elderly women.

INTRODUCTION

Frailty is a condition of increased susceptibility to stressors resulting from decreased physiological function and dysregulation of various body systems. The aging process is associated with an increase in proinflammatory markers' serum levels, indicating a chronic inflammatory process. These biological markers correlate with an increase in disability, mortality, and frailty.[1,2] Inflammation as a pathophysiological mechanism has been associated with loss of function or an increased risk of disease in an individual. Many geriatric syndromes are associated with a chronic inflammatory process.[3] The most common clinical manifestation of frailty is sarcopenia. Sarcopenia itself is a syndrome of loss of muscle mass, quality, and strength, which often occurs in the elderly and is considered a precursor syndrome or clinical manifestation of frailty. Increased serum proinflammatory cytokines in the elderly are associated with the reduction of skeletal muscles due to the aging process.[4,5] Some of the proinflammatory cytokines that also increase with the occurrence of this frailty syndrome are Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-α (TNF-α).[2,6,7]

Vitamin D and frailty are closely related to health in the elderly. The prevalence of frailty is around 10.7% in adults living in communities aged 65 years and over. 25-hydroxyvitamin D (25 (OH) D) deficiency is a potential risk factor for frailty, especially in the elderly. Vitamin D deficiency is associated with a risk of falling, which can speed up the frailty process. Vitamin D deficiency helps regulate inflammatory markers such as IL-2 and IL-12, and increases pro-inflammatory cytokines, leading to decreased muscle strength and poor physical performance including reduced leg strength, reduced grip strength, and short walking distances.[8] Review articles Jianghua, et al. states that there is a significant difference between serum 25 (OH) D levels and physical weakness in women compared to 25 (OH) D levels with physical weakness in men. Postmenopausal women are prone to sarcopenia, leading to functional impairment, physical disabilities and fractures. All of these things can worsen status frailty.[8]

The purpose of this study was to determine the relationship between IL-6, IL-1β and Vitamin D on frailty status in elderly women in elderly integrated health service (*posyandu lansia*), Semarang City.

METHOD

This study used cross sectional method with consecutive sampling method. The sample consisted of 27 elderly women over 60 years of age who were enrolled in integrated health service (posyandu)

Table 1. Sample characteristics

Characteristics	Total (N = 27)	%
Age		
60-69 years	18	66.7%
≥70 years	9	33.3%
Body mass index		
Normal	20	74.1%
Overweight-obese	7	25.9%
Blood pressure		
Normal	12	44.4%
Hypertension	15	55.5%
Vitamin D levels		
Adequate	1	3.7%
It's strong	6	22.2%
Deficiency	20	74.1%
IL-6		
High	14	51.9%
Low	13	48.1%
IL-1β		
High	12	44.4%
Low	15	55.6%

Table 2. Bivariate analysis of IL-6, IL-1β and vitamin D levels in the blood on frailty status in elderly women at Integrated health service for elderly (*posyandu lansia*) in Semarang City

Variable	Frailty status			p
	Fit N = 8	Pre Frail N = 16	Frail N = 3	
Vitamin D levels				
Adequate	0 (0%)	1 (3.7%)	0 (0%)	0.008
It's strong	5 (18.5%)	1 (3.7%)	0 (0%)	
Deficiency	3 (11.1%)	14 (51.9%)	3 (11.1%)	
IL-6				
High	3 (11.1%)	4 (14.8%)	0 (0%)	0.328
Low	5 (18.5%)	12 (44.4%)	3 (11.1%)	
IL-1β				
High	4 (14.8%)	6 (22.2%)	0 (0%)	0.095
Low	4 (14.8%)	10 (37%)	3 (11.1%)	

for elderly, Semarang City. Sampling was conducted in August 2018. Samples were recorded by posyandu officers and evaluated according to inclusion criteria. Samples were recruited after fulfilling predefined inclusion criteria, the inclusion criteria included: (1) women over 60 years of age, (2) able to communicate, (3) willing to participate in research. Meanwhile, the exclusion criteria established for sample elimination included: (1) still in an acute infection, (2) change residence

Samples from the study that met the inclusion criteria and were not included in the exclusion criteria were then measured for vital signs, weight and height measurements. The research sample was then taken venous blood to measure the pro-inflammatory cytokines IL-6, IL-1β and vitamin D. The optimal serum 25 (OH) vitamin D level is 25-80 ng/mL, although there are differences of opinion

regarding the definition of vitamin D deficiency (experts call deficiency if <30 ng/mL but other opinion said deficiency if <20 ng/mL).[9] The Cardiovascular Health Study Scale-based frailty questionnaire is a simple, noninvasive and validated screening tool to assess each component of frailty in the elderly. The status of frailty in the elderly can be categorized into three groups. The total number of frailty index values divided by 40 will result in the frailty score used in assessing the frailty status of the elderly. Elderly can be categorized as normal/fit/robust status if they have a score of ≤0.08, if they have a score > 0.08 <0.25, and the status is fragile/ frail if the score is ≥0.25. Filling out the questionnaire can be done independently by the elderly or conducted by interview by elderly posyandu officers.[10]

The data that has been collected is processed using the SPSS 25.0 program. The statistical analysis used was univariate and bivariate analysis. Univariate statistical analysis aims to describe the characteristics of each variable studied, while bivariate analysis aims to analyze the factors that are thought to be associated with frailty status in elderly women. The statistical test in this study used the Spearman correlation test.

RESULTS

A total of 27 samples were collected with the lowest age of 60 years and the highest 84 years, where the average age is 67.93 years. BMI status ranged from 18.7 kg/m$_2$ to 32.9 kg/m^2 with an average BMI of 23.84 kg/m^2. The results showed that as many as 55% of elderly women had hypertension. From all samples, it was found that 74.1% of elderly women had vitamin D deficiency. 51.9% of elderly women also had high levels of IL-6. In contrast to IL-1β levels, the results of this study indicated that elderly women tended to have low IL-1β levels, namely as much as 55.6% (Table 1).

From a total of 27 samples obtained, for the frailty status in elderly women, there were 8 people with fit status, 16 people had pre-frail status, and as many as 3 people had frail/robust status (Table 1 and Figure 1).

The bivariate analysis that has been carried out in this study, it was found that there was a significant relationship
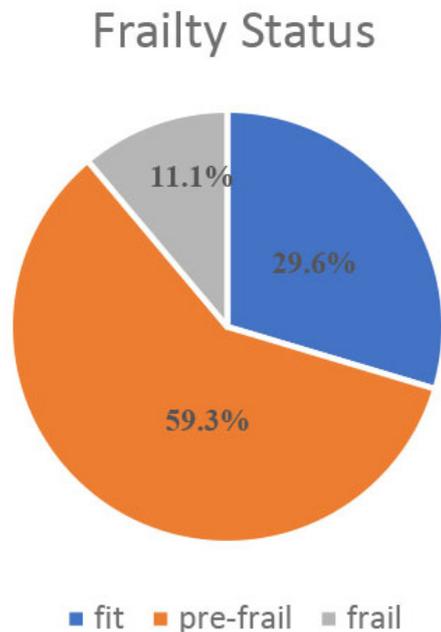
Frailty Status

Figure 1. Distribution of frailty status of elderly women in integrated health service for elderly (*posyandu lansia*) at Semarang City

between vitamin D levels in blood and frailty status (p=0.008; r=0.497) in elderly women, while in IL-6 (p=0.328) and IL-1β (p=0.095) was not shown to have a relationship with frailty status (Table 2).

DISCUSSION

Frailty has been described as a condition of increased susceptibility to stressors resulting from decreased physiological function and dysregulation of various systems in the body. The state of frailty results from the physiological accumulation of the aging process or related diseases from the decreased threshold of the body's physiological system which results in a worse level of health.[1,11,12] The composition of the elderly population is increasing rapidly in both developed and developing countries. This is due to a decrease in birth rates and mortality, along with an increase in life expectancy.[13] In this study, it was found that the highest age in elderly women was 84 years, which shows that life expectancy is increasing from year to year.In women at the age of 40, the frequency of ovulation starts to decrease and most of this will

stop in the next 15 years. When there is a decrease in estrogen levels, there are many cardiovascular events, decreased skeletal muscle mass, vasomotor instability, psychological symptoms and estrogen-responsive tissue atrophy.[14,15] This study found that there were more elderly women with hypertension, namely 15 people (55.5%) compared to elderly women who did not have a history of hypertension.

Proinflammatory cytokines that increase with age are associated with frailty such as tumor necrosis factor α (TNF-α), IL-6, IL-1 Ra, and chemokines C-reactive protein (CRP), IL-8, monocyte chemoattractants. protein-1 (MCP-1), and CXCL10, whereas cellular markers include white blood cells (WBC). Inflammation markers such as CRP and IL-6 were found to be higher in elderly with frailty and suggest that stimulation of the body's immune system by mild-chronic infection can be a predisposing factor for frailty.[16] The results of this study showed that as many as 51.9% of the elderly had high levels of IL-6, this is thought to be impaired by immune system regulation due to the aging process. The term immunosenescence is used to describe a decrease in the immune system's rate of response in elderly individuals and infection that occurs at a young age is thought to be a predisposing factor for immunosenescence in the elderly. IL-6 is a pro-inflammatory cytokine whose circulating levels in the blood increase with age. This is related to various pathophysiological processes such as malignancy, sarcopenia, decreased body function, disability and overall morbidity in elderly individuals.[16]

One of the biomarkers that increase in frailty conditions is interleukin-1β (IL-1β). Interleukin-1β stimulates an increase in the number of osteoclasts and an active resorption surface.[17] Interleukin-1β is a potent proinflammatory cytokine, which is crucial in the response of the host defense against infection or injury. The results of this study showed that 44.4% of individuals had high IL-1β levels with a prefrail status of 22.2%. This is due to the secretion process of IL-1β which is regulated by the strength of the inflammatory stimulus, and IL-1β levels are maintained to provide an adequate inflammatory response.[18]

Elderly is an independent risk factor for vitamin D deficiency.[19] So that the elderly, especially those with frailty conditions, tend to experience vitamin D deficiency, especially if the intake or intake of vitamin D is inadequate.[20] The results of this study are in accordance with the theory in which the number of elderly women with vitamin D deficiency is 74.1%. Meanwhile, only 1 elderly woman (3.7%) had adequate vitamin D levels. The relationship between the 25 (OH) D level and frailty is complicated. First, individuals with frailty may have difficulty getting outside from exposure to sunlight, which is the cause of low serum 25 (OH) D concentrations. Second, the binding of vitamin D with Vitamin D Receptor (VDR) can increase de novo synthesis of protein and cellular calcium absorption in muscle cells, thereby affecting muscle mass and performance. In addition, low levels of 25 (OH) D can activate vitamin D metabolites and reduce inflammatory mediators such as IL-2 and IL-12, consequently affecting physical performance and muscle strength. Third, weakness is closely related to vitamin D intake. Inadequate intake of vitamin D may worsen frailty status in subjects with low serum 25 (OH) D. Inadequate intake of vitamin D also increases the risk of falling, which can lead to status frailty. This is evident in this study that serum vitamin D levels have a significant relationship with frailty status (p=0.008; r=0.497) in elderly women. This is in line with research Zhou et al. states that there is a significant difference between serum 25 (OH) D levels and physical weakness in women compared to 25 (OH) D levels with physical weakness in men. Postmenopausal women are prone to sarcopenia, leading to functional impairment, physical disabilities and fractures. All of these things can worsen status frailty.[8]

CONCLUSION

The status of frailty in elderly women at Integrated health service for elderly (*posyandu lansia*) of Semarang City had pre-frail status, namely 59.3%. Vitamin D levels in the body have a significant relationship and unidirectional with frailty status in elderly women.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of this study.

ETHICAL CONSIDERATION

This research has been approved by Ethical Committee Faculty of Medicine Universitas Diponegoro-Dr. Kariadi Hospital, Semarang, Indonesia with ethical clearance reference number 141/EC/FK-RSDK/IV/2018. All study protocol in accordance to Helsinki declaration of human right. All study participants had received signed informed consent before any data collection.

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AUTHOR CONTRIBUTIONS

Dwi Ngestiningsih and Lusiana Batubara responsible for brainstorming the main idea, concept, writing the original draft, and supervision. Jessa Kris Dayanti responsible for data gathering and writing the original draft. All authors had reviewed the manuscript and agreed for final version of publication.

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