Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Sep 03; 10(B):2065-2069.
https://doi.org/10.3889/oamjms.2022.10414
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Geriatrics*

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Interleukin-6 Expression in Patients with Frailty Syndrome

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Edited by: https://publons.com/researcher/391987/mirko-spiroski
Citation: Nurmila N, Udaya W, Sudarso A, Bakri S, Rasyid H, Kasim H, Hardjianti T, Seweng A. Interleukin-6 Expression in Patients with Frailty Syndrome. Open Access Maced J Med Sci. 2022 Sep 03; 10(B):2065-2069. https://doi.org/10.3889/oamjms.2022.10414
Keywords: Frailty; Interleukin-6; Cardiovascular health study; Elderly
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Received: 14-Jun-2022
Revised: 08-Aug-2022
Accepted: 24-Aug-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

INTRODUCTION: Frailty is an age-related biological syndrome characterized by a decrease in physiological capacity and stress resistance resulting from a gradual decline in the body's physiological systems. Frailty syndrome patients are categorized into three groups: Robust/fit, prefrail, and frail. As a crucial immunosenescence aspect, chronic inflammation (systemic inflammation) characterizes aging. Proinflammatory cytokines, such as interleukin-6 (IL-6), increase in response to increasing molecular inflammation as individuals age. This study aimed to investigate IL-6 levels in older individuals dependent on their frailty status.

METHODS: This study used a cross-sectional design with 90 patients with frailty syndrome aged ≥60 who met the research requirements at our institution. The Cardiovascular Health Study scoring system was used to assess frailty syndrome. Statistical analyses used analysis of variance and Kruskal–Wallis tests, with a significance threshold of $p < 0.05$.

RESULTS: Males comprised most participants (54.4%). The most common form of weakness was frailty (43.3%). Frail individuals had significantly higher IL-6 levels (31.12 ± 13.40; $p < 0.001$) than prefrail (22.50 ± 3.29 ng/L) and robust (18.53 ± 2.04 ng/L) individuals. Individuals aged ≥70 had significantly higher IL-6 levels (27.01 ± 9.02 ng/L; $p < 0.05$) than those aged 60–69 (24.71 ± 10.94 ng/L). IL-6 levels only differed significantly between robust, pre-frail, and frail individuals aged 60–69.

CONCLUSIONS: IL-6 levels increased with frailty severity in individuals aged 60–69. However, IL-6 levels did not vary with frailty severity in individuals over 70.

Introduction

The elderly are those in the late adult stage that begins at age 60. The elderly population is increasing worldwide, including in Indonesia. The Jakarta Central Statistics Agency has estimated that about 29 million individuals aged ≥60 years will live in Indonesia in 2020–2025, representing about 11.11% of the total population, with an estimated life expectancy of 73.6 years and a higher proportion of older women (11.43%) than men (10.78%) [1].

Older adults with the pathological aging process are at risk of becoming frail elderly [2] In addition, frailty syndrome is often associated with disability. Therefore, it has a higher risk of decreased quality of life associated with poor health [2], [3]. Frailty is an age-related biological syndrome with decreased physiological capacity and resistance to stressors due to the accumulation of decline in various physiological systems of the body [4], [5].

Frailty syndrome classification is divided into three statuses, robust/fit, prefrail, and frail. The frailty syndrome diagnosis is based on Fried's phenotype with the cardiovascular health study (CHS) scoring system, consisting of five criteria: Low grip strength, slowed walking speed, low energy, low physical activity, and unintentional weight loss [6]. Older adults are said to be frail if they have ≥3 of these five criteria available, prefrail if they have 1–2 of these five criteria, and robust if they have none [7].

The causes of multifactorial frailty syndrome are genetics, the aging process, lifestyle, and other conditions that significantly influence frailty syndrome occurrence, such as inflammation [4]. Proinflammatory cytokines that increase with age are associated with frailty, such as interleukin-6 (IL-6) [8], [9]. The physiological role of IL-6 has been extensively studied in the context of frailty syndrome's acute phase. However, there is increasing evidence that IL-6 also plays a key role in chronic disease pathogenesis [8], [10]. This study determines IL-6 levels in the context of frailty status in the elderly.

Methods

Research methods

This study is an observational study with a cross-sectional approach conducted at the Geriatrics

Outpatient Department, Wahidin Sudirohusodo Hospital, Makassar, Indonesia, between May and November 2020. It was approved by the Health Research Ethics Committee of the Hasanuddin University Medical Faculty, Makassar, Indonesia (339/UN4.6.4.5.31/PP36/2021).

Study participants

Participants were elderly patients aged ≥60 years who sought treatment at the Geriatric Outpatient Department of Dr. Wahidin Sudirohusodo Hospital (Makassar, Indonesia) who meet the inclusion criteria: (1) Did not have Parkinson's disease; (2) did not have malignancy; (3) did not have acute arthritis; (4) did not have a cognitive impairment; (5) were not depressed; (6) agreed to participate in this study. Exclusion criteria included acute disorders (e.g., acute cerebrovascular events, severe infection, and acute cardiovascular events), cognitive impairment (i.e., a score of 7 on the Abbreviated Mental Test), and refusal to participate in the study.

Data Collection

Data were collected using interview methods, anthropometric measurements, handgrip strength dynamometer test, physical performance based on the "time up and go" test, muscle mass examination using a Bioelectrical Impedance analysis with the Tanita Type BC-418MA (Tanita Corporation; Tokyo, Japan), serum IL-6 assay, and frailty status assessment based on CHS criteria for Fried's phenotype [2], [11], [12], consisting of five criteria: Low grip strength, slowed walking speed, low energy, low physical activity, and unintentional weight loss.

IL-6 levels

Blood serum IL-6 levels were quantified using an enzyme-linked immunosorbent assay (ELISA). Briefly, about 3 mL of venous blood was drawn from each participant by the research assistant. Next, the serum was separated by centrifugation at 2000–3000 rpm for 20 minutes and stored at –80°C. Then, IL-6 levels were quantified (ng/L) using the Quantkin HS human IL-6 immunoassay (E0090Hu; R&D Systems; Minneapolis, MN, USA) with the ELISA method [13], [14]. The sensitivity of this assay is 1.03 ng/L, and its upper limit value in normal individuals is 7 ng/L.

Data analysis

Statistical analyses were performed using the SPSS v.22 (IBM SPSS; Armonk, NY, USA), including descriptive statistical calculations, frequency distributions, and Kruskal–Wallis and analysis of variance (ANOVA) tests. Data are presented as mean ± standard deviation (SD). All results with $p < 0.05$ were considered statistically significant.

Results

Participant characteristics

Participant characteristics are presented in Table 1. We found that females comprised over half of the participants (54.4%). Most participants were in the 60–69 age group (87.8%). Nearly half of the participants with frail status were in the frailty group (43.3%). Over two-thirds of participants had 1–3 comorbidities (68.8%). Almost half of the participants had a body mass index (BMI) that places them in the obesity 1 group (40.0%).

Table 1: Participant characteristics (n = 90)

Variable	N	%
Sex		
Male	41	45.6
Female	49	54.4
Age (years)		
60–69	79	87.8
≥70	11	12.2
BMI		
Underweight	2	2.2
Normal	23	25.6
Overweight	19	21.1
Obesity 1	36	40.0
Obesity 2	10	11.1
Low grip strength		
Yes	41	45.6
No	49	45.4
Unintentional weight loss		
Yes	12	13.1
No	78	86.1
Low energy		
Yes	17	18.9
No	73	81.1
Slow walking speed		
Yes	46	51.1
No	44	48.9 Low physical activity
Yes	8	8.9
No	82	91.1
Fraity status		
Robust	20	22.3
Prefrail	31	34.4
Frail	39	43.3
Number of comorbidities		
1–3	62	68.8
≥4	28	31.2
Serum IL-6 levels (ng/L; mean ± SD)	16.7–73.7 (25.4 ± 10.4)	

BMI: Body mass index, IL-6: Interleukin-6, SD: Standard deviation

Overview of serum IL-6 levels based on frailty status

Serum IL-6 levels associated with frailty status are presented in Table 2. The Kruskal–Walls test indicated that serum IL-6 levels differed significantly between the 20 participants with robust frailty status (18.53 ± 2.04), 31 participants with prefrail status (22.50 ± 3.29), and 39 participants with frail status (31.12 ± 13.40; $p < 0.001$).

Table 2: Overview of IL-6 levels based on frailty status

Variable	Robust (n = 20)	Prefrail (n = 31)	Frail (n = 39)	p-value*
IL-6 levels (ng/L; mean ± SD)	18.53 ± 2.04	22.50 ± 3.29	31.12 ± 13.40	0.001

IL-6: Interleukin-6, SD: Standard deviation, *: Kruskal-Wallis test.

Overview of serum IL-6 levels based on age

The relationship between serum IL-6 levels with age is shown in Table 3. We found that the mean IL-6 level in the 60–69 years groups (24.71 ± 10.94) differed significantly from the ≥70 years group (27.02 ± 9.02; $p < 0.05$).

Table 3: Overview of IL-6 levels based on age

Age (years)	n (%)	IL-6 levels (ng/L; mean ± SD)	p*
60–69	65 (72.2)	24.71 ± 10.94	0.009
≥70	25 (27.8)	27.01 ± 9.02	

IL-6: Interleukin-6, SD: Standard deviation; *Kruskal–Wallis test.

Correlation of serum IL-6 levels with frailty status and age

The relationship between frailty status and serum IL-6 levels when controlling for age is shown in Table 4. Serum IL-6 levels were significantly higher in frail participants (33.1 ± 16.1) than in robust participants (18.5 ± 2.0) aged 60–69 ($p < 0.001$). However, serum IL-6 levels did not differ significantly between frail and prefrail participants aged ≥70 ($p > 0.05$). Note that no robust participants were aged ≥70.

Table 4: IL-6 according to frailty status and age

Age (years)	Frailty status	n	IL-6 levels (ng/L; mean ± SD)	p*
60–69	Robust	20	18.5 ± 2.0	<0.001
	Prefrail	26	22.5 ± 3.5	
	Frail	19	33.1 ± 16.1	
≥70	Robust	0	–	0.187
	Prefrail	5	22.2 ± 2.0	
	Frail	20	28.2 ± 9.7	

IL-6: Interleukin-6, SD: Standard deviation, *: ANOVA test.

Discussion

Participant characteristics

In this study, females comprised over half of the participants (54.4%), consistent with Setiati *et al*. [1], whose study comprised 59.8% females and 40.2% males. Xue [2] found that females tended to be more flexible than males, with a prevalence of 30–48% in females and 21–35% in males. One influencing factor is the presence of the estrogen hormone condition, which reduces the IL-6 gene expression after menopause. Our participants were aged ≥60, with an average of 67.4 years. Most participants were aged 60–69 (87.8%). The Setiati *et al*. [7] study had a mean age of 72.4 years, with 35.3% of participants aged 60–69 years and 64.7% ≥70 years. In addition, the Cokorda *et al*. [7] study had a mean age of 67.5 ± 1.25 years.

Almost half of the participants had a BMI that placed them in the obesity 1 group (40.0%). Marfiani *et al*. [15] reported 18.4% obesity for the same age group as our study, and Sadjapong *et al*. [16] reported 14.5% obesity in Thailand. Nangoy and Kumala [6] explored the effect of physical activity on fat mass, finding that subjects with low physical activity had a 2.58-fold greater risk of excess fat mass than those with high physical activity.

Overview of frailty-based serum IL-6 levels

We quantified and compared serum IL-6 levels associated with frailty status. ANOVA and Kruskal–Wallis tests indicated that serum IL-6 levels increased significantly with worsening frailty status ($p < 0.001$). These results are consistent with Lee *et al*. [17], who suggested that IL-6 levels increased with frailty in Taiwan, and Ma [18], who found significantly higher IL-6 levels with frailty status ($p < 0.001$). The findings of this study also align with Epps *et al*. [19], who reported that IL-6 levels were significantly correlated with the three frailty statuses (robust, prefrail, and frail). However, its findings contrast with those of Lustosa *et al*. [20], who found no significant relationship between IL-6 levels and frailty status in Brazil ($p > 0.05$). Nevertheless, Lee *et al*. [21] suggested that high serum IL-6 levels are an overall causative risk factor for cardiovascular disease, cancer, and death.

Overview of age-based serum IL-6 levels

In this study, the average serum IL-6 level was found to be 24.71 ± 10.94 ng/L in participants aged 60–69 and 27.02 ± 9.02 ng/L in participants aged ≥70, differing significantly ($p < 0.05$). Most participants (65; 72.2%) were aged 60–69, compared to 25 (27.8%) aged ≥70, differing significantly. These differences accord with Setiati *et al*. [1], who found that individuals aged ≥70 tended to have frail compared to prefrail status. Age is one risk factor for frailty in the elderly. Another study by Corbi *et al*. [22] also found that individuals aged ≥70 years were more prone to frailty, albeit not significantly ($p = 0.018$).

In this study, serum IL-6 levels were found to increase with frailty status, differing significantly between participants with robust, prefrail, and frail status ($p < 0.001$). This finding is consistent with Lu *et al*. [23], who obtained IL-6 levels between 6.44 and 26.71 ng/ml (16.20 ± 4.40), suggesting that high IL-6 levels were more prevalent in frail than non-frail individuals and related to slower physical speed and lower and weaker physical activity. The results of this study indicate that IL-6 serum levels are significantly higher in individuals with frail status, consistent with Ma *et al*. [18], who found higher IL-6 levels in the elderly with frailty.

Correlation of serum IL-6 levels with frailty status

This study found that serum IL-6 levels were significantly correlated with frailty status in participants aged 60–69 ($p < 0.001$). This finding is consistent with Beharka *et al*. [24], who found elevated IL-6 levels in elderly individuals aged 65–85, increasing with worsening frailty.

Age-based serum IL-6 levels were found not to be significantly associated with frailty status in participants aged ≥70 ($p = 0.187$). Therefore, the relationship of serum IL-6 levels with age and frailty status is independent. Ershler *et al*. [25] found that many healthy elderly individuals had elevated IL-6 levels, requiring early intervention to prevent bad frailty-related outcomes.

A comparison of serum IL-6 levels with frailty status controlling for age found significant differences between robust, prefrail, and frail participants aged 60–69. This finding is consistent with Epps *et al*. [18], who found that frailty status was strongly associated with the inflammatory index, including IL-6 levels, which increased with age.

This study had several limitations. Our small sample size and cross-sectional study design means that we cannot infer directional correlations. Given the low level of involvement, there may have been selection bias. However, since our study's prevalence results are consistent with the previous studies, we expect that any response or selection biases have not caused them to be under or overestimated.

Conclusions

Serum IL-6 levels increased with worsening frailty in participants aged 60–69. However, they did not differ significantly by frailty status in participants aged ≥70.

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