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Plasma Sirt-1 Level in Various Frailty Degree in Elderly Outpatients at Prof. Chairudin P. Lubis Hospital, Medan

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Abstract Frailty, a syndrome linked to the physical aging process, manifests as vulnerability to health decline, diagnosed based on criteria like frailty, reduced walking speed, fatigue, diminished physical activity, and weight loss. SIRT1, pivotal in elderly frailty, acts protectively against frailty, offering a promising therapeutic modality. This study was an observational study with cross-sectional design. The subjects were 118 outpatients in polyclinics of Prof. Chairuddin P Lubis Hospital, Medan with the age of 60 years old and above who were recruited from December 2022-January 2023 through consecutive sampling. Frailty was measured using Frailty Index-40 item (FI-40) questionnaire with the frailty scale defined as robust (0), pre-frailty (1-2), and frailty (3-5) and plasma sirtuin 1 level was measured using ELISA technique. Most of the subjects (45,7 %) were pre-frail, 33,8 % and 20,3 % subject were frail and robust, respectively. There was a slightly higher mean SIRT1 levels in frail subjects compared to pre-frail and robust, but not statistically significant. We concluded that there was a trend increase of plasma sirtuin 1 level in frail subjects. Further study is suggested to consider the composition of diets.

Keyword: Frailty, Sirt1, Elderly

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1 Introduction

One in every five elderly individuals in Indonesia faces a range of serious problems, including frailty, functional dependency, malnutrition risk, depression, history of falls, prior hospitalization, and polypharmacy, all of which are associated with the condition of frailty [1]. To understand the root causes of aging related to the accumulation of genetic mutations, in-depth research is needed to unravel mechanisms capable of reversing the aging process and identifying frailty-related biomarkers [2]. The identification of frailty-related biomarkers is of utmost importance to deepen the understanding of this disorder and to assist in early diagnosis, appropriate interventions, and frailty management [3].

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Physical weakness increases with age, affecting 4-59% of elderly individuals in the community and being more common in women. Its prevalence is influenced by chronic conditions such as depression, nutrition, socioeconomic status, and education [4]. SIRT1 plays a crucial role in longevity through calorie restriction, being high in young individuals [5]. Studies in India have shown a decline in plasma SIRT1 with age related to weakness and cognitive impairment [6]. found that frail elderly men have lower plasma SIRT1 levels, which are associated with nutritional status and body composition [7].

Frailty syndrome associated with aging diminishes physical capability and health vulnerability. Symptoms include weakness, fatigue, medical complexity, and medical procedure intolerance. Appropriate management enhances recovery in vulnerable patients [20]. Frailty syndrome slows movement, induces fatigue, and causes weight loss. Timely intervention is crucial to mitigate adverse effects on the elderly by detecting and monitoring biomarkers related to complex weakness. However, some biomarkers associated with aging have limitations as disease predictors [1].

The classification of frailty encompasses various levels, including robust, pre-frail, and frail. This classification aids in assessing risks and planning appropriate care for each individual, as follows: 1) Robust: Individuals who are in good physical and mental condition, exhibiting no significant signs of physical or cognitive vulnerability; 2) Pre-frail: Individuals displaying early signs of physical weakness, functional decline, or loss of independence. They may experience physical decline, reduced endurance, or fatigue; 3) Frail: Individuals experiencing significant levels of vulnerability and weakness, often characterized by severe physical and cognitive decline. They are prone to injuries, illnesses, or dependence [19].

Sirtuin is an anti-aging therapy targeted with deacylase and/or ADP ribosyltransferase protein activities, regulating aging and related diseases. SIRT1 combats aging, obesity, and diseases by repairing proteins. The levels of SIRT1 protein are associated with cardiovascular diseases in the elderly, indicating a significant role in aging-related disease therapy. SIRT1 also influences frailty in the elderly and can be enhanced through nutritional status for health interventions. SIRT6, along with SIRT1, enhances health and physical activity, reducing frailty in old age [21], [6].

Many studies employ genomic, transcriptomic, metabolomic, and proteomic analyzes to uncover accurate frailty biomarkers [8, 9]. Proteomic research on frailty biomarkers is relatively limited, with small subject sizes ([10,11], High-temperature requirement serine protease A1 (HtrA1) [12], Glycoproteins [13, 14]), and Sirtuins (SIRT1) [15, 16]. However, research findings have contributed to a better understanding of the proteomic characteristics underlying frailty [5]. The sirtuin (SIRT1), which plays a crucial role in calorie restriction-induced longevity, and has higher circulating levels in younger individual [5], has also been demonstrated to serve as a potential aging biomarker in experimental animal models [17, 18]. Therefore, plasma sirtuin level is the

potential as a biomarker for frailty. To confirm this hypothesis, in this study we observed the correlation between plasma Sirt-1 level and frailty in the elderly.

2 Method

This was an observational study with a cross-sectional design. A total of 118 outpatients from polyclinics at Prof. Chairuddin P. Lubis Hospital in Medan with the age 60 year old and above were participated in this study. The subjects were recruited consecutively from December 2022 until January 2023. Patients with acute illness and refused to participate in the study were excluded.

Demographic data such as age, gender, formal education, ethnicity, and marital status were obtained from medical records. Blood plasma from the patients were aliquoted from blood collection during routine laboratory test and proceeded for Sirt1 level quantification using Human SIRT1 ELISA Kit from Elabscience (Cat.No.:E-EL-H1546). Frailty was determined using Frailty Index-40 item (FI-40) questionnaire with the frailty scale defined as 0= robust, 1-2= pre-frailty, and 3-5= frailty.

Ethical approval for this study was obtained from Ethics Committee for Health Research of Universitas Sumatera Utara (No. 1097/KEPK/USU/2022) and based on the Nuremberg Code and Helsinki Declaration.

3 Results

Age and gender of subjects were obtained from medical record confirmed with direct interview (Tabel 1).

Table 1. Patient Characteristics Based on Age and Sex

Characteristics	N	%
Age (year)		
<60	5	4.23
60-65	57	48.30
66-70	36	30.53
71-75	14	11.86
76-80	6	5.08
Sex		
Male	60	50.85
Female	58	49.15

In Table 1, it is shown that the most dominant age group among subjects was 60-65 years old, comprising a total of 57 individuals (48.30%), while the most dominant gender was male, accounting for 60 individuals (50.85%).

Frailty scale was determined using *Frailty Index-40 item (FI-40) questionnaire* that measures the scores in 5 components i.e Fatigue, Resistance, Ambulatory, Ilnesses and Loss of weight. Based on the total score obtained, subjects were classified under 3 groups of frailty as shown in table 2.

Table 2. Distribution based on the frailty scale of subjects.

Characteristics	**N**	**%**
Robust	40	33.8%
Pre-frail	54	45.7%
Frail	24	20.3%
Total	**118**	**100%**

Table 2 shows the dominant characteristic of subjects based on frailty is the pre-frail with a total of 54 individuals (45.7%), robust with 40 individuals (33.8%), and frail with 24 individuals (20.3%).

Plasma Sirtuin 1 level from subjects was measured with ELISA method and compared among 3 frailty scale groups. Mean and standard deviation of plasma sirtuin 1 level in robust, pre frail and frail subjects were 48,09 ± 26,82 ng/ml, 58,27 ± 22,55 ng/ml and 59,28 ± 28,81 ng/ml, respectively. Data was analysed using one way ANOVA and showed no statistically significance in plasma sirtuin level among goups (figure 1). However there was a trend that plasma sirtuin 1 level in frail subjects were slightly higher than prefrail and frail subjects.

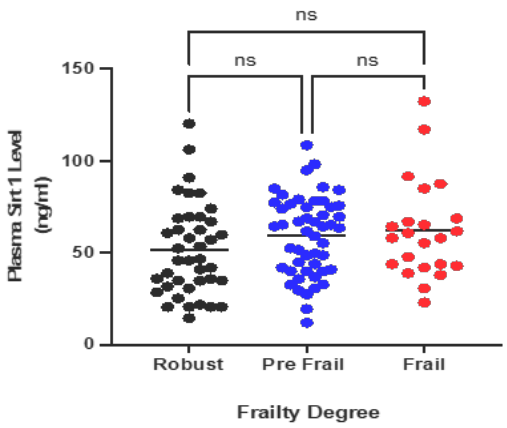

Figure 1. Difference of Sirtuin 1 levels across various Frailty categories
One way ANOVA test, p>0,05

4 Discussion

In this study, the results of the Pearson correlation test show No There is connection between plasma SIRT1 levels with level weak -positive frailty (r = 0.177) and not significant (p=0.055) where n value 0.177 indicates a positive relationship between the two variables. Apart from that, the results of the F test showed a significant simultaneous relationship between plasma SIRT1

levels and *frailty* . However , the plasma levels of SIRT1 were significantly lower in frail elderly subjects compared to non-frail elderly subjects, even after adjusting for various subject characteristics such as age, gender, diabetes mellitus, hypertension, cognitive impairment, and the number of comorbidities. Specifically, plasma SIRT1 levels also decreased in elderly subjects with a history of or currently experiencing heart disease, heart attacks, congestive heart failure, kidney disease, and joint pain. However, the levels were even lower in individuals who were frail and had diabetes or a history of stroke. Furthermore, plasma SIRT1 levels decreased with advancing age and the number of comorbidities, with a more pronounced decline in frail subjects compared to non-frail elderly individuals. Notably, SIRT1 levels were lower in the frail group compared to the non-frail group.

This research are related to the research by Elibol & Kilic, which states that there is a significant increase in the SIRT1 levels in the elderly. The oldest individuals (76.0 ± 1.5 years) with the highest SIRT1 level (4.61 ± 0.32) demonstrate a correlation with longevity. Additionally, the levels of OSI are higher and PON-1 levels are lower in the elderly compared to adults and children. This could explain the elevated SIRT1 protein levels as a compensatory mechanism for oxidative stress in the elderly. Aging is the active continuation of genetically programmed development in an organism. Genetic studies on longevity genes and their relationship with phenotypes, including our current findings, represent the first study demonstrating age-related changes in crucial SIRT1 levels for healthy aging by controlling gene-environment interactions at an early age. Therefore, further research is needed on the relationship between genetic and epigenetic mechanisms for SIRT1 to enhance the quality of life in the elderly by reducing the burden of age-related chronic diseases through lifestyle changes and dietary habits [22].

However, the study by Zotti et al, indicates that the phenotype outcomes of frail subjects are still far from a satisfactory definition. The study reported mood, cognition, and quality of life (QoL) data in relation to anamnestic factors, health, and socioeconomic status in the FRASNET geriatric population (1204 subjects in stable health conditions). This population represents an observational cohort study that includes a fairly balanced group of Italian subjects classified as frail (421, 35%), pre-frail (449, 37.3%), and robust (334, 27.7%) [23].

Furthermore, literature suggests that elevated SIRT1 levels may upregulate genes associated with neuronal protection [24, 25, 26]. However, SIRT1 exhibits a dual role in responding to inflammation, acting as a double-edged sword in neurodegeneration. Low SIRT1 levels contribute to early acute inflammation-induced tissue damage by boosting NF-kB, while high SIRT1 levels during late inflammation lead to immunosuppression and increased mortality [27]. A previous study found that enhancing SIRT1 expression alone is insufficient for safeguarding the brain from neurodegeneration; an increase in SIRT1 activity is also crucial. For instance, Ciriello and colleagues observed a notable reduction in phosphorylated SIRT1, the active form, in multiple sclerosis patients [28]. Interestingly, a significant negative correlation between

phosphorylated and non-phosphorylated SIRT1 forms was identified, elucidating both SIRT1 overexpression and its inactivity in diseased states. Furthermore, administering a SIRT1-activating compound demonstrated profound therapeutic benefits and neuroprotective effects against age-related neurodegenerative diseases [29].

These findings are consistent with the study conducted by Le Couteur et al, which validated the results using SPR technology with Western blot analysis, considered the gold standard for protein analysis. The study conducted on the CHAMP population assessed SIRT1 expression in SK Hep1 cells cultured with serum samples obtained from frail and non-frail individuals. Unfortunately, no direct correlation was found between frailty and SIRT1 expression in these cells. Post hoc analysis suggested a potential paradoxical relationship between low SIRT1 expression induced by serum and frailty. The authors of the CHAMP study also acknowledged that their results were unexpected, as high tissue expression of SIRT1 is generally considered beneficial, influenced by calorie restriction, and expected to be higher in younger subjects [15].

However, frail older adults exhibited notably elevated Serum SIRT1 levels compared to their more robust counterparts. Among older individuals experiencing slowness or weight loss, heightened SIRT1 levels were observed. Notably, the correlation between Serum SIRT1 levels and reduced gait speed persisted even after adjusting for factors such as age, sex, insulin, vaspin, leptin levels, and negative correlation with phospholipase A2 levels. The study identified a connection between elevated SIRT1 levels in frail elderly individuals and a decline in physical function. The findings suggest that insulin and adipokine levels may serve as a link between SIRT1 and frailty, while inflammation may not play a significant role in this relationship [30].

5 Conclusion

Most of the subjects were in the group of “pre-frail”. There was no statistically significant difference in plasma sirtuin 1 level among subjects in different frailty groups. Further study is suggested to consider the diet and supplementation that are taken by the subjects. High flavonoid diets can increase plasma level of sirtuin 1.

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