



# Correlation Study between Serum Cytokines TNF- $\alpha$ , IL-6, IL-15 Levels and Sarcopenia

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## Abstract

**Aims:** To investigate the pathogenesis of sarcopenia and the role of important cytokines TNF- $\alpha$ , IL-6, and IL-15 in patients with sarcopenia by measuring their levels. **Methods:** During September to December 2020, a total of 200 healthy individuals were randomly selected as research subjects from those who were undergoing physical examinations at Linyi People's Hospital. These subjects were divided into three groups, with 155 cases in the non-sarcopenia group (Group 1), 25 cases in the pre-sarcopenia group (Group 2), and 20 cases in the sarcopenia group (Group 3). The skeletal muscle content of the limbs was accurately measured using bioelectrical impedance analysis (BIA) technology. The levels of three cytokines TNF- $\alpha$ , IL-6, and IL-15 in the peripheral venous blood serum, which are closely related to skeletal muscle mass, underwent quantitative detection by applying the enzyme-linked immunosorbent assay (ELISA). **Results:** The IL-15 level in the non-sarcopenia group was significantly higher than that in the sarcopenia group, and the difference was statistically significant ( $P < 0.05$ ). However, there was no significant statistical difference in the levels of TNF- $\alpha$  and IL-6 among the three groups. **Conclusion:** IL-15 may play an important role in the occurrence and development of sarcopenia, and its decreased level may be related to the progression of sarcopenia.

## Subject Areas

Clinical Medicine

## Keywords

Sarcopenia, IL-15, IL-6, TNF- $\alpha$ , Cytokines

## 1. Introduction

Sarcopenia, a concept first proposed by Irwin Rosenberg in 1989, describes the changes in body composition and function that occur with increasing age [1]. Subsequently, relevant working groups have been established in various countries and regions, the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS), and the Asian Working Group for Sarcopenia (AWGS). They have published and updated the diagnostic and treatment consensus for sarcopenia, thus promoting the understanding and attention of medical workers and the public to sarcopenia.

With the development of China's economy, lifestyle and population structure changes have made musculoskeletal diseases a significant public health concern, and sarcopenia demands adequate attention. This study aimed to measure and analyze TNF- $\alpha$ , IL-6, and IL-15 using statistical methods to explore their mechanisms and associated factors in sarcopenia, thereby laying a foundation for clinical diagnosis and treatment and uncovering the pathological pathway.

## 2. Materials and Methods

### 2.1. Research Subjects

According to the sarcopenia diagnostic criteria of AWGS 2019 [2] and the pre-sarcopenia criteria of EWGSOP [3], during September to December 2020, a total of 200 healthy individuals were randomly selected as research subjects from those who were undergoing physical examinations at Linyi People's Hospital. These subjects were divided into three groups, with 155 cases in the non-sarcopenia group (Group 1), 25 cases in the pre-sarcopenia group (Group 2), and 20 cases in the sarcopenia group (Group 3). This study was approved by the Ethics Committee of Linyi People's Hospital. After fully notifying the participants of all study details, such as purpose, procedures, potential risks and benefits, they voluntarily gave their informed consent to participate.

Inclusion criteria: 1) Age  $\geq$  18 years; 2) Normal limb movement, without osteoarthritis, hemiplegia, limb amputation, etc.; 3) Able to perform muscle strength and physical function tests.

Exclusion criteria: 1) Pregnant or lactating women; 2) Individuals with implanted electronic devices; 3) Patients with autoimmune diseases; 4) Cancer patients or those with a history of cancer; 5) Patients with acute infections, severe liver and kidney diseases, respiratory and cardiovascular and cerebrovascular diseases; 6) Those who have long-term used growth hormones, glucocorticoids, sex hormones and other drugs.

### 2.2. Research Materials and Methods

- Examination and Cytokine Determination:

The skeletal muscle content of the limbs was measured with the InBody770 body composition analyzer manufactured by Biospace. The grip strength was

assessed using the WCS-100 electronic grip dynamometer from Shanghai Xinman Science and Education Equipment Co., Ltd. After the subjects fasted overnight for over 8 hours, 5 ml of venous blood was drawn from the elbow in the morning. The blood was left to stand at room temperature for approximately 120 minutes to allow clot formation, and then centrifuged at 4°C at 1600 r/min for 15 - 20 minutes. The supernatant serum was collected and stored in a -80°C freezer. The levels of three cytokines TNF- $\alpha$ , IL-6, and IL-15 in the peripheral serum, which are closely associated with skeletal muscle mass, were determined by enzyme-linked immunosorbent assay (ELISA). The ELISA kits were supplied by Ailaisa Biotechnology (Shanghai) Co., Ltd.

- Sarcopenia Diagnostic Criteria:

The definitive diagnosis of sarcopenia necessitates fulfilling the criteria of diminished limb skeletal muscle content, accompanied by a reduction in muscle strength or/and physical function.

- 1) Determination of Limb Skeletal Muscle Mass

The assessment of limb skeletal muscle mass is conducted in the following manner: When employing dual-energy X-ray absorptiometry (DXA), a limb skeletal muscle mass of less than 7.0 kg/m<sup>2</sup> in men and less than 5.4 kg/m<sup>2</sup> in women is considered a reduction. Similarly, with bioelectrical impedance analysis (BIA) technology, a limb skeletal muscle mass below 7.0 kg/m<sup>2</sup> for men and under 5.7 kg/m<sup>2</sup> for women is also regarded as a decrease.

- 2) Evaluation of Muscle Strength

Muscle strength is gauged such that a grip strength of less than 28 kg in men and less than 18 kg in women is deemed a decline.

- 3) Physical Function Testing

Physical function is tested where a 6-meter walking speed slower than 1 m/s, or a 5-sit-up time reaching or exceeding 12 seconds, or a Short Physical Performance Battery (SPPB) score of 9 or less indicates a decrease.

- Pre-sarcopenia Diagnostic Criteria:

Only a decrease in muscle mass, without a decrease in muscle strength and physical function.

- Data Statistical Processing

SPSS 25.0 was used. The measurement data were expressed in the form of ( $\bar{x} \pm s$ ). Analysis of variance was used to compare the differences, with a P-value less than 0.05 considered statistically significant.

### 3. Results

The average IL-15 in the non-sarcopenia group was (11.83  $\pm$  6.41) pg/ml, the average IL-15 in the pre-sarcopenia group was (10.85  $\pm$  7.15) pg/ml, and the average IL-15 in the sarcopenia group was (7.23  $\pm$  6.19) pg/ml. The distribution of the average IL-15 in the three groups was different, and the difference was statistically significant (P < 0.05). Among them, the IL-15 in the non-sarcopenia group was greater than that in the sarcopenia group, and the difference was statistically

significant ( $P < 0.05$ ); there was no statistically significant difference between the non-sarcopenia group and the pre-sarcopenia group ( $P > 0.05$ ), and there was no statistically significant difference between the sarcopenia group and the pre-sarcopenia group ( $P > 0.05$ ). In this experimental group, the average values of TNF- $\alpha$  and IL-6 had no statistical significance ( $P > 0.05$ ) (See **Table 1** and **Table 2**).

**Table 1.** Distribution of some cytokines among the three groups.

	Group 1	Group 2	Group 3	F	P
TNF- $\alpha$ (pg/ml)	24.83 $\pm$ 21.84	28.5 $\pm$ 28.39	31.47 $\pm$ 17.77	0.964	0.383
IL-15 (pg/ml)	11.83 $\pm$ 6.41	10.85 $\pm$ 7.15	7.23 $\pm$ 6.19	4.518	0.012
IL-6 (pg/ml)	7.81 $\pm$ 6.74	6.89 $\pm$ 6.21	5.38 $\pm$ 2.42	1.390	0.251

**Table 2.** Comparison of IL-15 between groups.

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	Standard Error	P	95% Confidence Interval	
IL-15 (pg/ml)	1	2	0.983	1.397	0.482	-1.770	3.740
	1	3	4.601	1.540	0.003	1.560	7.640
	2	3	3.618	1.945	0.064	-0.220	7.450

#### 4. Discussion

The experimental results demonstrated that the average IL-15 level in the non-sarcopenia group was (11.83  $\pm$  6.41) pg/ml, that in the pre-sarcopenia group was (10.85  $\pm$  7.15) pg/ml, and that in the sarcopenia group was (7.23  $\pm$  6.19) pg/ml. The distribution of the average IL-15 levels among the three groups was different, and the difference was statistically significant ( $P < 0.05$ ). This suggests that IL-15 may have a certain association with the occurrence and development of sarcopenia. The IL-15 level in the non-sarcopenia group was higher than that in the sarcopenia group, and the difference was statistically significant ( $P < 0.05$ ), indicating that a higher level of IL-15 may have a protective effect on muscles or be related to the maintenance of normal muscle metabolism and function. Combined with previous studies, IL-15 as a myokine released by skeletal muscles, can inhibit the catabolic process in skeletal muscles, promote the synthesis of skeletal muscles, and hinder fat deposition in the body [4]. In outpatient elderly people, a lower level of IL-15 in plasma has been associated with sarcopenia [5]. This is in line with the relationship between IL-15 and sarcopenia observed in this experiment, further supporting the potential role of IL-15 in sarcopenia.

However, there was no statistically significant difference between the pre-sarcopenia group and the non-sarcopenia group or the sarcopenia group ( $P > 0.05$ ), which may imply that during the development of sarcopenia, the change in IL-15 is a gradual process, and no obvious change may have occurred in the pre-sarcopenia stage.

In addition, in this experiment, the average values of TNF- $\alpha$  and IL-6 did not show statistical significance ( $P > 0.05$ ). TNF- $\alpha$  is a pro-inflammatory cytokine that can act on skeletal muscles, leading to a decrease in muscle strength. Skeletal muscle fibers express two types of TNF- $\alpha$  receptors, namely TNFR1 and TNFR2. *In vitro* experiments have shown that the reaction of muscles to TNF- $\alpha$  is mainly mediated through the activation of TNFR1 [6], but a meta-analysis by Tuttle *et al.* indicated that systemic TNFR2 levels have a stronger association with lower muscle strength and quality [7]. As for IL-6, it is a key cytokine involved in low-grade chronic inflammation, expressed in fibroblasts, macrophages, and vascular endothelial cells, etc. It can be detected in the circulatory system after physical exercise. As a myokine, it can regulate muscle metabolism, and a continuous high level will lead to muscle atrophy [8]. However, in this experiment, these two cytokines did not show significant differences, which may be related to various factors such as sample size, individual differences of research subjects, and experimental environment. Future studies may consider expanding the sample size, refining the grouping criteria, and comprehensively considering potential confounding factors such as age, sex, exercise level, and diet to more accurately explore the relationship between TNF- $\alpha$  and IL-6 and sarcopenia [9].

This experiment provides valuable references for in-depth understanding of the roles of cytokines related to sarcopenia. However, more in-depth and comprehensive studies are still needed to further clarify their internal mechanisms and inter-relationships.

## 5. Conclusion

This study examined and analyzed the non-sarcopenia, pre-sarcopenia, and sarcopenia groups. A statistically significant difference was found in the IL-15 level between the non-sarcopenia and sarcopenia groups, with the non-sarcopenia group having a higher level. This suggests that IL-15 may be important in the occurrence and development of sarcopenia, and its level change may be closely related to the progression of the disease. However, TNF- $\alpha$  and I-6 did not show significant differences among the three groups, which may be due to factors such as a small sample size and differences in research methods. Future research should expand the sample size and use more uniform and precise research methods to deeply investigate the complex role mechanisms of these cytokines in sarcopenia, thereby providing a more reliable theoretical basis and practical guidance for the early diagnosis, effective prevention, and accurate treatment of sarcopenia.

## Conflicts of Interest

The authors declare no conflicts of interest.

## References

- [1] Rosenberg, I.H. (1997) Sarcopenia: Origins and Clinical Relevance. *The Journal of Nutrition*, **127**, 990S-991S. <https://doi.org/10.1093/jn/127.5.990s>

- [2] Chen, L., Woo, J., Assantachai, P., Auyeung, T., Chou, M., Iijima, K., *et al.* (2020) Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *Journal of the American Medical Directors Association*, **21**, 300-307.e2. <https://doi.org/10.1016/j.jamda.2019.12.012>
- [3] Cruz-Jentoft, A.J., Baeyens, J.P., Bauer, J.M., Boirie, Y., Cederholm, T., Landi, F., *et al.* (2010) Sarcopenia: European Consensus on Definition and Diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing*, **39**, 412-423. <https://doi.org/10.1093/ageing/afq034>
- [4] Quinn, L.S., Anderson, B.G., Strait-Bodey, L. and Wolden-Hanson, T. (2010) Serum and Muscle Interleukin-15 Levels Decrease in Aging Mice: Correlation with Declines in Soluble Interleukin-15 Receptor Alpha Expression. *Experimental Gerontology*, **45**, 106-112. <https://doi.org/10.1016/j.exger.2009.10.012>
- [5] Yalcin, A., Silay, K., Balik, A.R., Avcioglu, G. and Aydin, A.S. (2017) The Relationship between Plasma Interleukin-15 Levels and Sarcopenia in Outpatient Older People. *Ageing Clinical and Experimental Research*, **30**, 783-790. <https://doi.org/10.1007/s40520-017-0848-y>
- [6] Hardin, B.J., Campbell, K.S., Smith, J.D., Arbogast, S., Smith, J., Moylan, J.S., *et al.* (2008) TNF- $\alpha$  Acts via TNFR1 and Muscle-Derived Oxidants to Depress Myofibrillar Force in Murine Skeletal Muscle. *Journal of Applied Physiology*, **104**, 694-699. <https://doi.org/10.1152/jappphysiol.00898.2007>
- [7] Tuttle, C.S.L., Thang, L.A.N. and Maier, A.B. (2020) Markers of Inflammation and Their Association with Muscle Strength and Mass: A Systematic Review and Meta-analysis. *Ageing Research Reviews*, **64**, Article ID: 101185. <https://doi.org/10.1016/j.arr.2020.101185>
- [8] Belizário, J.E., Fontes-Oliveira, C.C., Borges, J.P., Kashiabara, J.A. and Vannier, E. (2016) Skeletal Muscle Wasting and Renewal: A Pivotal Role of Myokine IL-6. *Springerplus*, **5**, 619. <https://doi.org/10.1186/s40064-016-2197-2>
- [9] Witham, M.D., Achison, M., Aspray, T.J., Avenell, A., Band, M.M., Donnan, P.T., *et al.* (2021) Recruitment Strategies for Sarcopenia Trials: Lessons from the LACE Randomized Controlled Trial. *JCSM Rapid Communications*, **4**, 93-102. <https://doi.org/10.1002/rco2.38>