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REVIEW

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Biomarkers of sarcopenia: an unmet need

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Abstract

Background Sarcopenia is a syndrome characterized by a progressive decline in muscle mass and strength, with subsequent deterioration of functional performance and increased morbidity and mortality. Its emergence may be associated with disorders that are not limited to the elderly. The multifactorial nature of sarcopenia is a major barrier to diagnosis. Several risk factors contribute to the development of sarcopenia, including age, gender, and amount of physical activity. Additionally, the pathophysiology of sarcopenia involves inflammatory conditions, endocrinal dysfunction, and metabolic alterations. Several studies have proposed numerous molecules that may be linked to the pathogenesis of sarcopenia and could be useful in the future; however, there is an unmet need to discover a sensitive, reliable, and cost-effective biomarker of muscle aging.

Main text The objective of this research is to highlight different biomarkers of sarcopenia that reflect its multifactorial pathophysiology. A narrative review was carried out through a series of literature searches in the database MEDLINE/PubMed focusing on sarcopenia biomarkers. The following search terms were used: "sarcopenia," "osteosarcopenia," "muscle ageing," "muscle failure," "sarcopenic obesity," "weakness," "biomarkers," "frailty," "comorbidity," "functional disability," and "inflamm-aging." The studies were observational and peer-reviewed. They were all carried out at a referral center, hospital, or in the community. The articles chosen all contained information about sarcopenia. Case reports and articles that did not assess people's muscle aging and sarcopenia were not considered.

Conclusion Despite the availability of numerous functional, imaging, and biological sarcopenia markers, the inherent limitations of the assessment tools make it difficult to objectively measure the various sarcopenia domains. A valid and reliable biomarker of sarcopenia has yet to be identified. The identification of "gold standard" evaluation techniques that should be systematically used is also impacted by the variability of the populations to be assessed. In this context, the establishment of an international consensus adopting a multi-biomarker approach may be of utmost importance to tackle the different aspects of this multifactorial health-related problem.

Keywords Sarcopenia, Frailty, Biomarkers, Aging, Inflamm-aging, Diagnosis

Background

Sarcopenia is a disorder characterized by a generalized decline in muscle mass and strength. It is directly linked to physical impairment, poor quality of life, and high mortality. Although it is primarily a disease of the elderly, other disorders, such as inflammatory conditions, inactivity, and malnutrition, may also contribute to its development [1].

According to reports, sarcopenia affects 5 to 13% of people between the ages of 60 and 70, but it affects 11 to 50% of people over the age of 80. Since the age of 40, people begin to lose 1% to 2% of their muscle annually. At age 70, skeletal muscle mass declines by 25–30%, and muscle strength declines even more noticeably by up to 40% [2].

In 1989, Rosenberg used the term "sarcopenia" (Greek: "sarx" or flesh + "penia" or loss) to describe this age-related loss of muscle mass [3]. In 2008, the term

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dynapenia was proposed to describe age-related loss of muscle strength in the absence of neurological or muscular disorder. It was linked to the functional impairment of the neuromuscular apparatus [4]. Over the upcoming decades, although many committees published their consensus diagnostic definition of sarcopenia, the most widely recognized one was that proposed by the European Working Group on Sarcopenia in Older People (EWGCOP) [5]. The first definition of sarcopenia that was published by EWGSOP in 2010 aided in the identification and care of people at risk of or suffering from sarcopenia. This operational definition by EWGSOP states that low muscle mass and poor physical performance are necessary for the diagnosis of sarcopenia [6]. Eight years later, an update (EWGSOP2) was released as many aspects of sarcopenia and muscle role in health and diseases were explored. Muscle strength was placed at the top of the diagnostic algorithm, and several measures of muscle strength, muscle mass, and/or physical performance were included with gender-specific cut-off points for some of these measurements for diagnosing sarcopenia in daily clinical practice. Furthermore, EWGSOP2 advised using the sarcopenia questionnaire (SARC-F questionnaire) as a formal method of collecting self-reports from patients with symptoms suggestive of sarcopenia [7].

The multifactorial nature of sarcopenia presents the most difficult diagnostic challenge. There are many risk factors for sarcopenia including age, gender, and level of physical activity [1, 8]. Sarcopenia could be either age-related (primary sarcopenia) or disease-related (secondary sarcopenia). The age-related loss of skeletal muscle mass is caused by a decrease in the number of myofibers and the atrophy of individual myofibers. It affects mainly the fast-twitch muscles in a slow, progressive course, and subsequently, these changes are irreversible [9]. While secondary sarcopenia is mainly due to a decrease in the cross-sectional area of myofibers, it tends to affect the slow-twitch muscles in an acute and severe manner; however, these changes are usually reversible [10]. Moreover, it has been reported that aging is associated with a progressive reduction in the number of motor units and morphological changes in neuromuscular synapses [11]. Additionally, protein synthesis in muscle decreases with aging, and protein anabolism is suppressed in the muscles of the elderly even when the same amounts of amino acids are present in the blood, which is known as anabolic resistance [12]. All the aforementioned changes result in the functional decline of skeletal muscles and muscle atrophy.

Moreover, the pathophysiology of sarcopenia includes inflammatory conditions, obesity and endocrinal dysfunction. Furthermore, muscle-related myokines and cytokines have been linked to autocrine regulation of muscle metabolism, as well as paracrine and endocrine effects on other tissues like bones and fats, a phenomenon known as bone, muscle, and fat cross-talk. A number of chronic diseases and sedentary lifestyle factors (such as malnutrition, obesity, and lack of physical activity) may also contribute to the development of sarcopenia [13–16].

Despite recent advances in the assessment of muscle mass and strength, the numerous mechanisms underlying the development and prediction of sarcopenia are not fully understood; however, a series of biomarkers that may potentially help characterize the different mechanisms of sarcopenia allows for the identification of those with early sarcopenia and the implementation of a personalized, effective management strategy for the optimal prevention, and treatment of those patients [16–18].

Main text

Method: search strategy

A narrative review was carried out by conducting a series of literature searches in the database MEDLINE/PubMed for English language articles focusing on sarcopenia biomarkers. A combination of medical subject headings and keywords was used in the search strategy. The following search terms were used: "sarcopenia," "osteosarcopenia," "muscle ageing," "muscle failure," "sarcopenic obesity," "weakness," "biomarkers," "frailty," "comorbidity," "functional disability," "inflamm-aging," and "apoptosis." Sources published within the last 7 years were given preference. The researchers extracted data using a standardized data collection form, which was then discussed among the authors. The studies were observational and peer-reviewed. The studies were all carried out at a referral center, hospital, or in the community. The articles chosen all contained information about sarcopenia. Case reports and articles that did not assess people's muscle health and sarcopenia were not considered.

Biomarkers of sarcopenia

Actually, the skeletal muscle is no longer considered a simple contractile tissue but an interface of more complex connections. In addition to muscle loss and contractile dysfunction, sarcopenia also includes metabolic and endocrinal alterations as well as low-grade age-related systemic inflammation (also known as "inflamm-aging"). The process of muscle loss involves a significant decline in protein regeneration coupled with an accelerated protein lysis and apoptosis [19–21].

A biomarker was defined by the National Institutes of Health Biomarkers Definitions Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic

processes, or pharmacologic responses to a therapeutic intervention." [22]. According to this definition, the term biomarker refers to a broad sub-category of medical signs that can be measured accurately and with reproducibility. A biomarker could be a simple clinical tool, a specific molecule in the biofluid, or an imaging biomarker where a specific biological feature could be detected by imaging. Specific sarcopenia biomarkers that might be linked to clinical evaluation allow for the detection of subjects suffering from or at risk of developing sarcopenia as well as the monitoring of the efficacy of preventative and therapeutic measures. The ideal biomarker of sarcopenia needs to be accurate, specific, reliable, cost-effective, and available [16, 18]. In the next section, we will discuss some of the biomarkers of sarcopenia based on different pathophysiologic mechanisms.

Muscle mass biomarkers

Muscle mass is the amount of skeletal muscles in the body, while lean body mass refers to the non-adipose tissue mass (total body weight − body fat weight). Several tools, such as anthropometric parameters (e.g., calf circumference, mid-arm muscle circumference), bioelectric impedance analysis (BIA), imaging techniques, and biochemical markers, are used to objectively assess muscle mass [18, 23, 24] (Table 1).

Imaging biomarkers such as dual-energy X-ray absorptiometry (DXA), ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) are commonly used to qualify muscle or lean body mass. These imaging techniques can provide measures of muscle mass, muscle cross-sectional area (CSA), and muscle density. Skeletal muscle index (SMI) is an important parameter in the assessment of muscle mass. It is calculated by dividing the total appendicular skeletal mass (ASM) (kg) by standing height (m^2) [27, 28].

However, each imaging technique has significant shortcomings. Actually, body thickness, hydration level, and extracellular fluid buildup have a significant negative impact on the DXA results. Additionally, DXA cannot quantify intramuscular adipose tissue. On the other hand, high costs, and complicated technology, prevent the widespread use of CT and MRI. The test subject receives substantial doses of ionizing radiation from CT as well. [18] Using anthropometry, BIA, or ultrasonography, although cost-effective and commonly applicable, is either inaccurate or not adequately standardized to be used as a diagnostic tool. This paved the way for the creation and validation of new muscle mass biomarkers that can be measured in biofluid samples and used economically to detect and monitor the condition. Such biochemical markers would also make healthcare professionals more knowledgeable about sarcopenia, eventually encouraging its inclusion in best practices [31].

Muscle-specific biomarkers such as Procollagen type III N-terminal peptide (P3NP), peptides derived from collagen type VI turnover, and skeletal muscle-specific isoform of troponin T (sTnT) were investigated as potential biomarkers of loss of muscle mass, however, their lack of specificity limits their use as reliable makers of sarcopenia [32–34].

A recently developed method for precisely measuring total body muscle mass is the D3-creatine dilution method. The technique uses creatine's irreversible conversion to creatinine and the latter's excretion in urine to estimate the size of the total body creatine pool as an analog for the total mass of skeletal muscles. This method's estimates of the total body muscle mass exhibit remarkable agreement with whole-body MRI scans [35]. Unlike the DXA, the D3-creatine dilution method's measurement of muscle mass is strongly positively correlated with physical performance and predicts incidents of falls and functional decline [36–39]. However, urinary creatine excretion is also altered in other organ dysfunctions, such as testicular damage [40].

Members of the transforming growth factor (TGF) superfamily, myostatin, and growth differentiation factor-15 (GDF-15), are antagonists of skeletal muscle myogenesis and growth inhibitors. Myostatin is a myokine secreted from muscle cells and adipose tissues and is involved in the pathogenesis of sarcopenia [41]. The use of antibodies against myostatin was found to improve muscle mass and grip strength [42]. A myostatin inhibitor called folistatin (FST) appears to be an intriguing tool for assessing the amount of muscle damage [43].

Irisin (IR) is a peptide secreted by the skeletal muscles, particularly after exercise. It is produced by the cleavage of a fibronectin type III domain-containing protein 5 (FNDC5). It may be classified as an adipomyokine, as it is secreted by the adipose tissues. Studies demonstrated a significant correlation between the circulating levels of IR, lean mass, and hand grip strength [44]. Interestingly, both obese patients and healthy individuals showed a direct correlation between IR and FST. Additionally, it was found that the expression of IR mRNA positively correlated with FST mRNA expression in muscular biopsies from both groups [45]. These results are very intriguing because they highlight the potential existence of a quiet, mutual relationship between FST and IR in skeletal muscles.

Cathepsin D is an aspartic endopeptidase, a type of lysosomal proteolytic enzyme found in all animal cells. The level of cathepsin D has been found to be significantly higher in the serum of sarcopenic patients relative

Table 1 Biomarkers of muscle mass

Biomarker	Technique	Cut-off value
Anthropometric measures		
Calf circumference (CC)	Measure the calf circumference at the greatest point (left leg for right handed subjects, and vice versa), while sitting, knee at ankle are at right angle and foot on the ground. Done with a non-elastic plastic tape. The measurement is taken on bare skin [25]	> 31 cm is indicative of low muscle mass (recommended by WHO Expert Committee) [25]
Mid-arm circumference (MAMC)	Measure the mid-arm circumference (non-dominant hand) with a non-elastic plastic tape, at the mid-point between the olecranon process and the acromion of the shoulder. The triceps skinfold thickness is measured using a calibrated skinfold caliper MAMC = mid-arm circumference–(3.14 × triceps skinfold thickness) [26]	Only one study determined cutoff values for sarcopenia ranging from 21.0 to 24.9 cm in men and 19.8 to 23.3 cm in women [26]
Bioelectric impendence analysis (BIA)	Measurements are taken between the right wrist and ankle with the subject in a supine position Measurement of body composition compartments and calculation of the appendicular skeletal mass (ASM) [24]	Low muscle mass is considered when SMI less than 7 kg/m^2 in men and 5.5 kg/m^2 in women, according to the EWGSOP2 [7]
Dual-energy X-ray absorptiometry (DXA)	Measurement of body composition compartments and calculation of the appendicular skeletal mass (ASM) [27]	
Computed tomography (CT)	Calculate the CSA of: • The Abdominal muscle mass at the third or fourth or fourth lumbar vertebra • The psoas muscle Examine for intramuscular fat (Myosteatosis). [27, 28]	Muscular CSA must be adjusted for height to determine the SMI. (CSA/height^2) - SMI cut-off values for men range from 52 to 55 cm^2/m^2 and 39 to 41 cm^2/m^2 for women [29]
Ultrasonography (US)	Assess cross-sectional area, muscle thickness, echo intensity, fascicular length, contrast-enhanced vascularization, and elastography The anterior compartment of the thigh is an excellent anatomical location to take US measurements [27, 28]	No standard cut-off value
Magnetic resonance imaging (MRI)	Provide information about muscular edema, fibrous substitution, and muscular elasticity and contraction [28] Magnetic resonance spectroscopy (MRS) analysis assesses muscle quality (intermuscular and intramyocellular lipid depots) [30] No standard imaging protocol	No standard cut-off value
muscle-specific biomarkers • Procollagen type III N-terminal peptide (P3NP) • Peptides derived from the collagen type VI turnover • Skeletal muscle-specific isoform of troponin T • D3-creatine dilution method • Irisin • Cathepsin D		No standard cut-off value
Transforming growth factor (TGF) superfamily myostatin and growth differentiation factor-15 (GDF-15)		No standard cut-off value

to normal people [46]. Moreover, a negative relationship was reported between cathepsin D levels and gait speed [46]. In a recent study, when a predictive model with cathepsin D, age, and BMI was created (AUC = 0.908) to enhance its diagnostic performance, the sarcopenia group had levels of cathepsin D that were 2.2 times higher than the control group [47].

Muscle strength biomarkers

Muscle strength is defined as the amount of force generated by a dynamic muscle contraction [48]. The most popular, simple, and widely used tests for assessment of muscle strength of the upper and lower limbs are the Isometric handgrip strength (IHG) by hand dynamometer and the five-time sit-to-stand test (5STS) [49]. Other tests such as isokinetic knee extension and flexion strength have been evaluated in clinical research as predictors of sarcopenia (Table 2).

Low IHG has been associated with poor physical activity, and mobility impairment in cross-sectional [51–53] and prospective studies [54, 55]. Moreover, in a study including a well-functioning elderly population, low muscle mass did not explain the strong relationship between strength and mortality, indicating that when estimating the risk of events, muscle strength could be more significant than muscle mass [56]. Additionally, the strong correlations between IHG and lower extremity muscle power, knee extension torque, and calf cross-sectional muscle area highlight the fact that sarcopenia is a generalized rather than a localized disorder [57].

Isokinetic dynamometry is used mainly to assess muscle strength in athletes. Particularly in elderly people with sarcopenia, it can give valuable data about muscle strength [58]. It focuses on lower extremity musculature such as knee extensors and flexors. Isokinetic knee extension strength was measured as a parameter of muscle strength in several studies with participants in a sitting position; the most commonly used angular velocity was 60°/s, and peak torque (Nm) was the most commonly recorded measure [50, 53]. However, cut-off values for knee extension strength are lacking.

Functional biomarkers

Around the third decade of life, physical function starts to decline, with a more severe decrease occurring after the age of 50, which raises the possibility that the initial decline in physical performance may be an early indicator of sarcopenia [59]. However, the term "physical performance" refers to a broad concept that encompasses a number of elements, not just muscle power, strength, and mobility.

Physical performance tests are used in conjunction with muscle strength and mass measurements. They include the gait speed, the Short Physical Performance Battery (SPPB), and the stair climb power test (Table 3). A strong correlation was found between physical performance measures, body composition, and skeletal muscle parameters [60, 61]. In addition, they have the ability to predict health-related outcomes, such as mortality, morbidity, and disability [62–65]. SPPB in particular had proven to be a reliable and sensitive tool (sensitivity 82%) in diagnosing severe sarcopenia when using the cut-point of ≤ 8 [66]. Unfortunately, each has its own characteristics and only captures specific aspects of muscle functioning, resulting in different sets of possibilities in sarcopenia measurement.

Non-specific sarcopenia biomarkers

Inflammatory biomarkers

Aging is characterized by a state of low-grade systemic inflammation called "inflamm-aging" phenomenon [70]. In this situation, pro-inflammatory cytokines are unregulated, with subsequent decreased anti-inflammatory cytokine levels. Inflammatory aging contributes to accelerated muscle loss and prevents muscle regeneration, which promotes sarcopenia [71]. Actually, decreased muscle mass, strength, and physical function are closely linked to elevated levels of C-reactive protein, tumor necrosis factor, interleukin-8, interleukin-6, granulocyte-monocyte colony-stimulating factor, interferon, and high-temperature requirement serine protease A1 in older adults [72, 73].

Table 2 Biomarkers of muscle strength

Test	Technique	Cut-off value
Isometric handgrip strength (IHG)	The dynamometer is held in the dominant hand with the base resting in the palm 5-s maximal isometric contraction [49]	< 27 kg and < 16 kg in men and women respectively (by EWGSOP2) [49]
Five-time sit-to-stand test (5STS)	Time needed to rise from a seated position five times without support [49]	> 15 s for five rises [49]
Isokinetic knee extension strength	Measure knee extension strength by isokinetic dynamometry in a sitting position [50]	No cut-off value

Table 3 Biomarkers of functional performance

Test	Technique	Cut-off value
Gait speed		≤ 0.8 m/s
Timed Get Up-and-Go (TGUG) **test**	Time needed to rise from a seated position and walk for 3 m away and return back seated [67]	≥ 20 s [67]
Short physical performance battery	- Time of 4 m walking - Side by side feet stand for 10 s - Semi tandem stand for 10 s - Tandem stand for 10 s - Chair stand as above - Each component scored on a scale of 0–4 with 0 = test failure and 4 = full achievement [68]	8 points [68]
Stair Climb Power Test (SCPT)	Timed climb of a flight of stairs (4-11 stairs) Power in watts = [(body weight in kg) × (9.8 m/s^2) × (stair height in meters)]/(time in seconds) [69]	No cut-off value (varied with age)

Hormonal biomarkers

There is a great deal of evidence that changes in sex hormone levels in the blood may be linked to defects in muscle protein homeostasis. A significant decline in hormonal levels may contribute to a reduction in the ability to synthesize proteins and repair muscle damage with subsequent muscle mass loss, which implies a gradual shifting towards the catabolic state. Studies have shown that the onset of sarcopenia is influenced by sex hormones, particularly testosterone and dehydroepiandrosterone sulfate (DHEAS), whose levels decline with age [74]. Testosterone has anti-catabolic, anti-inflammatory, and anabolic effects on muscle [75]. DHEAS may have an impact on how well muscles function, and its age-related decline is a significant contributor to the loss of muscle mass and strength in older people [74]. Insulin-like growth factor 1 (IGF-1), and growth hormone (GH) levels are also reduced in sarcopenia. IGF-1 is an anabolic hormone that promotes muscle regeneration and mediates the effects of GH. IGF-1 administration has been shown to speed up the functional recovery of injured skeletal muscle [76].

Neuromuscular junction (NMJ) dysfunction biomarkers

Dysfunction of the NMJ is one of the symptoms of sarcopenia [77]. Studies showed that people who are sarcopenic have significantly more circulating C-terminal agrin fragments (CAF) than people who are not sarcopenic [78, 79]. Agrin binds to acetylcholine receptors at the postsynaptic terminal, where it aggregates them as a crucial part of the neuromuscular junction. Agrin is cleaved into CAF22 by proteolytic cleavage in sarcopenia and other catabolic disorders, which results in dysfunction of the NMJ. In patients with pulmonary diseases, sarcopenia has been linked to an increase in CAF22 levels [80]. Furthermore, serum CAF22 levels were consistently higher in accelerated sarcopenic patients than in healthy subjects. However, serum CAF22 levels did not correlate with either the SPPB or the SARC-F questionnaire [17].

Metabolic biomarkers

Several metabolic biomarkers known as metabolomics were strongly linked with muscle mass and quality in the elderly. In particular, lower plasma concentrations of the branched-chain amino acids leucine and isoleucine were found in sarcopenic older individuals [81]. Additionally, it was reported that the circulating levels of essential amino acids were lower in frail older people compared to their non-frail peers [82].

The gut microbiota appears to play a role in regulating several muscle metabolic pathways [83]. However, the causal correlations between age-related changes in muscles and gut microbiota had not been clearly investigated. The age-related disruption of the barrier function of the gut mucosa and subsequent gut dysbiosis may trigger inflammation and contribute to immune system dysregulation [84]. Animal studies demonstrated that a lack of gut microbiota was associated with a reduction in muscle mass [85, 86]. Similarly, studies on antibiotics that alter the microbiota, such as metronidazole, found a significant decrease in muscle mass in the hind limb and muscle fiber volume in the tibialis anterior muscle of mice. In vitro studies have also revealed that gut microbial products like indoxyl sulfate and p-cresol sulfate can have a direct effect on muscle mass [87].

Artificial intelligence (AI) as a biomarker of sarcopenia

In 2021, Chung et al. developed an AI diagnostic model of sarcopenia using transcriptome datasets that include a large number of different genes in muscle biopsies from sarcopenic patients and age-matched healthy subjects across three different ethnic groups. The model had the ability to successfully diagnose sarcopenia accurately

(100% sensitivity, 94.12% specificity, and 95.83% accuracy) [88]. Moreover, AI may have a valuable role in the accurate measurement of imaging parameters of sarcopenia, such as abdominal musculature segmentation with deep learning, which provides a great chance to assess muscle mass and myosteatosis independently [29, 89]. It is worth noting that AI-assisted body composition measurement would improve the efficacy and accuracy of the sarcopenia assessment, decrease the inter-examiner variability, and aid in the establishment of normal reference cut-off values for different populations using a broader set of data via an AI-assisted technique, which could have a role in the development of standardized assessments [90–93].

Conclusion

The broad concept of a sarcopenia biomarker as an objective tool that can assess different sarcopenia domains with precision and reproducibility has allowed different clinical, laboratory, and imaging tools to emerge as potentially promising sarcopenia biomarkers. However, most of these tools lack a standardized quantitative cutoff value to define sarcopenia, which seems essential to predicting early sarcopenia and determining the treatment threshold.

Furthermore, it is challenging to accurately and consistently measure various aspects of sarcopenia due to the inherent limitations of the current assessment tools, such as their lack of specificity and variability based on different population characteristics. In this context, the establishment of an international consensus adopting a multi-biomarker approach may be of utmost importance to tackle the different aspects of this multifactorial health-related problem.

Abbreviations

AI	Artificial intelligence
ASM	Appendicular skeletal mass
AUC	Area under the ROC curve
BIA	Bioelectric impedance analysis
CAF	C-terminal agrin fragments
CC	Calf circumference
CSA	Cross-sectional areas
CT	Computed tomography
DHEAS	Dehydroepiandrosterone sulfate
DXA	Dual-energy X-ray absorptiometry
EWGCOP	European Working Group on Sarcopenia in Older People
FNDC5	Fibronectin type III domain-containing protein 5
FST	Folistatin
GDF-15	Growth differentiation factor-15
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
IHG	Isometric handgrip strength
IR	Irisin
NMJ	Neuromuscular junction
MAMC	Mid-arm circumference
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
P3NP	Procollagen type III N-terminal peptide
SARC-F	Sarcopenia questionnaire
SMI	Skeletal muscle index
SPPB	Short Physical Performance Battery
STnT	Skeletal muscle-specific isoform of troponin T
TGF	Transforming growth factor
US	Ultrasonography.
5STS	Five-time sit-to-stand test
°/s	Degree per second

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