



THE IMPACT OF AGE-RELATED SARCOPENIA ON SURVIVAL AND MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT:

There is an increasing HF population resulting from the higher number of MI survivors and the widespread presence of diabetes, hypertension, CHD (Chronic Heart Failure), obesity and other chronic conditions. Cardiac dysfunction is the main factor that leads to reduced physical activity in patients with HF. The alternations in skeletal musculature often are present in the background of HF and can contribute to fatigue and dyspnea. Sarcopenia is a reduction in muscle mass and force, and it is right to say that it is one of the signs of “getting old”. The modern views on sarcopenia are that it is an outcome of many medical, behavioral and ecological factors, which are common in older people. Together with a sedentary lifestyle, it can be the main reason for disability in the late stages of human life. In our study, we examined the significance of reduced skeletal muscle tissue on mortality and survival of patients with diagnosed HF. The results showed that sarcopenia is a significant contributing factor for increased mortality [$p = 0,022$] and reduced survival rates [$p = 0,033$] in patients with HF II – IV class by NYHA. As a secondary goal we found there is significant correlation between age and sarcopenia [$R^2_{Linear} = 0,057$].

Keywords: Chronic Heart Failure (CHF), Sarcopenia, Ageing, Mortality,

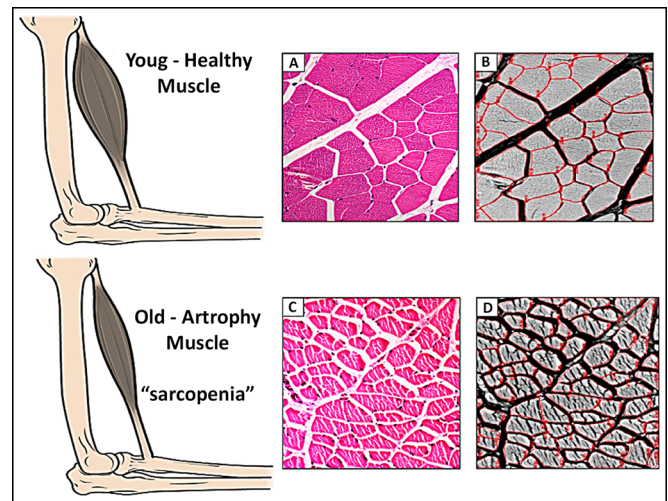
INTRODUCTION:

There is an increasing HF (Heart Failure) population resulting from the higher number of MI survivors, the widespread presence of diabetes, hypertension, CKD (Chronic Kidney Disease), obesity and other chronic conditions. Cardiac dysfunction is the main factor that leads to reduced physical activity in patients with HF. The alternations in skeletal musculature often are present in the background of HF and can also contribute to fatigue and dyspnea [1]. “Cardiac skeletal myopathy” in older age combined with sarcopenia can lead to more severe functional impairment. [2] Two-thirds of the cases with advanced HF have muscle fiber atrophy, reduced capillary density, the bolder shape of the myofibers secondary to myofiber edema and accumulation of fibrosis and adipose tissue. The alternations in muscle morphology and fiber

orientation leads to a further reduction in force generation capacity.

The nature of muscle changes in sarcopenia is different. During aging, there is selective denervation and loss of fast motor units, fibers of type 2 are more prone to atrophy than type 1 fibers. There is a 26% reduction in the cross section of fibers of 80-year-olds compared to those of 20-year-olds. After the age of 80, both types of fibers decrease. Denervation and loss of fast motor units start from 60 years of age with around 3% tissue loss per year, which leads to up to 60% loss of fibers at the age of 80 or above. Adipose and fibrosis infiltration are other important factors for muscle quality changes. Fig. 1 [3]

Fig. 1. Changes in muscle structure in sarcopenia.[3]



The selective advantage of bigger muscle mass in the late Paleolithic age can be the main reason for the increased death rate from sarcopenia, which is observed in many actual epidemiological studies. The discrepancy between our genome and a relatively sedentary lifestyle can be an important factor in the inappropriately low gene expression of certain genes (for example, gene α -actin) and lead to progressive muscle mass reduction. Although it's hard to directly prove that hypothesis, it can give valuable information on the molecular basis of sarcopenia.

Drugs and nutrition have the potential to impact positively or negatively the progression of sarcopenia. For example, NSAID (Non-steroid anti-inflammatory drugs), usually used by older people, can lead to the worsening of sarcopenia. The trials conducted among young, healthy males show that NSAID are inclined to go through a protein synthesis reaction, which is naturally present after eccentric exercise due to inhibition of the prostaglandin signals. It is yet unclear that the same effects are present in older people with or without HF.

The effect of nutrition on skeletal muscle metabolism is not fully clear yet. The connection between protein intake and muscle mass is only a hypothesis. Some early reports don't show a significant effect of protein intake on muscle mass and force in the elderly. Some newer data show that nutrition supplements, in addition to a physical exercise regime, can prove useful for delaying sarcopenia progression. [4, 5, 6]

Patients with HF develop anorexia as a result of nausea and secondary gastropathy due to intestine edema, which leads to malabsorption. Also, some of the drugs prescribed for HF can lead to loss of appetite, such as ACE-I and β -blockers. In addition, diuretics can promote electrolyte loss with urine. To summarize, the inadequate intake of basic elements and their loss makes HF prone to malnutrition and makes way for muscle depletion.

Another possible mechanism, which can explain sarcopenia, is the catabolic effect of chronic inflammation. The catabolic effects of anti-inflammatory cytokines like TNF- α , IL-1, IL-6 and of the muscle fibers are studied in *in vivo* and *in vitro* trials [7].

Epidemiological trials show that muscle force and, in less, muscle mass are connected with the levels of circulating IL-6 and TNF- α [7]. Ferrucci and colleagues show that the serum levels of IL-6 are a predictor of loss of muscle tissue force in elderly women. IL-6 also has a negative role in muscle force [8]. In summary, these results show that inflammation is an important reason of sarcopenia. In fact, IL-6 and IL-1 secretion is the main mechanism in the turnover of the muscle cell as the answer to micro trauma after physical exercise. Inflammation markers usually are elevated in patients with HF. Inflammation also is part of the pathogenesis of sarcopenia. It is a fundamental common factor between the two conditions. More specific, TNF- α and its soluble receptors promote muscle mass reduction and force during five year follow-up among more than 2000 adults participating in the Health ABC study. Among the possible reasons for TNF- α elevation in HF is the endotoxin hypothesis. This suggests that intestinal edema, which is common in HF patients, will change permeability to endotoxin-like lipopolysaccharide (LPS), a powerful inflammatory stimulator and inductor of the monocyte activation. At last, even if TNF- α production is controlled mainly by mononuclear cells, the super expression is supported by catecholamines, and their concentrations are higher in HF patients as an answer to myocardial damage and peripheral tissue hypoxia.

Shaap et al. observe that higher levels of IL-6 and CRP increase the risk of muscle force loss in a longitudinal trial about aging in Amsterdam. IL-1, IL-6 and TNF- α are linked with UPS and can induce anorexia and lipolysis, which leads to loss of body mass. If this thesis proves right, it can open new therapeutic options. The newest data show that high levels of physical activity are linked with lower levels of circulating inflammation markers. This is in contrast with the fact that after vigorous physical activity, the serum levels of anti-inflammatory cytokines are extremely elevated [7, 9]. It is proved thought that the peak levels of cytokines after exercise routine in people with a systemic exercise regime are becoming lower with time. In the same group, the overall levels of serum cytokines also become lower at rest. [10, 11]. This is a possible mechanism for prophylactics for sarcopenia, especially in those with CHF.

Catabolism versus Anabolism, individual skeletal muscle mass is the balance between synthesis and degradation of muscle protein. The latest trials are focused on signal pathways, which are included in the genesis of muscle hypertrophy and atrophy. More specifically, these trials are focused on identifying potential pharmacological targets. The first trial about signal pathways concerning muscle mass is conducted among patients with HIV and cancer. Lately, more specialists are focused on aging and sarcopenia, also sarcopenia and heart failure. Because of the super-expression of insulin-like growth factor - I (IGFI) in compensatory hypertrophy, its role is studied in many trials [10]. There is an idea that IGFI can be useful in the treatment of sarcopenia because it can directly stimulate the satellite cells and activate the chain signal pathways, which encourage cell proliferation. Age-related reduction of growth hormone and the levels of IGFI, are linked with reduced muscle mass and function.

Ghrelin is a peptide hormone produced mainly in the belly area. It has a pleiotropic effect, including stimulation of growth hormone secretion. Lately, ghrelin has drawn attention because, as it seems, it inhibits the sympathetic nervous system activity through vasodilatation in order regulation of appetite without growth hormone mechanisms and also to inhibit anti-inflammatory cytokines [10]. Ghrelin also down-regulates the secretion of leptin. (an (ob) gene product which reduces food intake and increases the energy expense for rest, and regulates tissue growth factor-beta one (TGF- β 1)). [11]

Testosterone is studied as a possible factor in sarcopenia. Low levels of testosterone are common in patients with HF, and it is believed that this helps for myocardial dysfunction through peripheral vascular resistance alternation, increased cardio-vascular load and cardiac output.

Angiotensin II is not only dependable for blood pressure control and heart muscle remodeling. It also plays a role in muscle mass loss. In such a model, the loss of muscle tissue is mainly due to UPS (Ubiquitin-proteasome system) mediated protein degradation. Other ambulatory trials show that the implementation of ACE-inhibitors or ARBs decreases the level of myocyte

apoptosis and generates mitochondrial free radicals. At the same time, they improve NO synthesis and expression of mammalian rapamycin target (MOTR) in old rats. [12]

Another option in sarcopenia control is the ubiquitin-proteasome pathway, which includes two genes that are linked with skeletal muscle atrophy. These genes, MuRF1 and MAFbx, are super-regulated during the process of skeletal muscle atrophy and code ubiquitin ligases. These ligases connect and mediate ubiquitination of myofibril protein for upcoming degradation during muscle atrophy. Ubiquitin seems important for the catabolic activity of many inflammatory cytokines which belong to the IL-6 superfamily [13]. Is UPS active in the sarcopenic muscle, that is still in discussion. The conducted trials show a different increase in UPS activity, in some significant, in others mild to none. [14]

Myostatin, also known as grow factor 8, is a down-regulator of muscle mass. Myostatin is mainly expressed in skeletal muscle tissue as an inductor for muscle atrophy. Myostatin is also expressed in the myocardium, where it has an anti-hypertrophic effect but also a pro-fibrotic one. Myostatin-inhibiting and blocking agents should be carefully studied in pre-clinical models before their safety and efficacy are determined in clinical trials in men. [9]

In the last decade, there has been a hypothesis for accelerated elimination of nucleus cells due to apoptosis as a mechanism for sarcopenia. Several apoptosis pathways are linked age related muscle atrophy. In private, the TNF- α mediated pathway of apoptosis is active in the skeletal muscles of elderly rodents, which suggests its possible role in age related muscle loss. [15]. A higher frequency of myocyte apoptosis is present in HF patients compared to healthy controls at the same age [15]. In the same trial, cardiac cachexia is not linked with an increase in myocyte apoptosis but is linked with increased fibrosis, which suggests a different mechanism of muscle waste in HF patients and those with cachexia.

In normal physiological conditions, anaerobic metabolism generates a small amount of reactive oxygen species (ROS), which are rapidly detoxified by antioxidant systems. When there is a dis-balance between pro-oxidants and antioxidants, oxidative stress is present. The production of ROS increases with age, and it suggests that it is a factor in aging. ROS can accelerate muscle protein degradation as they accumulate during contractile activity. Muscle enzyme systems (Catalase, glutathione transferase, superoxide dismutase) are decreasing with age.

There is no evidence that ROS production and oxidative stress increase with aging, but there is convincing data that tissue concentrations of serum antioxidant acceptors, especially superoxydismutase (SOD), increase with age. Although older people have increased antioxidant activity, it may not be enough to protect the muscles from ROS.

Because of the multifactorial character of sarcopenia, there is an increasing demand for focused and complex studies in this area. Understanding the mechanisms,

which lead to age-related and HF-related sarcopenia, can be a key to developing new effective treatments that can improve patients' quality of life.

The reduction of skeletal muscle mass has a negative impact on metabolism, adaptation and immunological answer to the disease, reducing the ability of our organism to withstand the changes in the environment. Sarcopenia is a strong predictor of death rate independent of all other known risk factors and diseases.

Study Goal:

The goal of our study is to examine the role of sarcopenia in HF and to compare the mortality and survival rate between HF non-sarcopenia patients and those with HF and sarcopenia in a group of patients with HF II-IV class by NYHA tested positive for sarcopenia through CT tissue densitometry. We have examined also the correlation between sarcopenia, age and NT-pro BNP as a secondary goal.

METHODS:

Overall, we used documental and sociological, clinical, instrumental and statistical methods including survival analysis, correlations and Kaplan Meyer curves, to help us design, carry out and finish our study; The statistical analysis was made with IBM SPSS Statistics 23.

RESULTS AND DISCUSSION

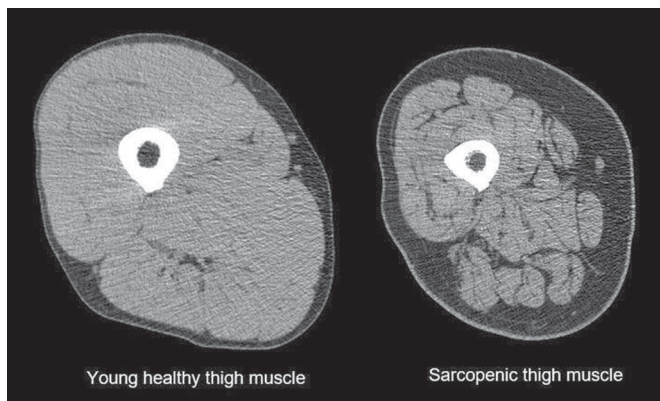
We created a group of patients, subsequently admitted to the clinic with HF, who fulfilled all the including criteria (Age ≥ 18 y/o, present HF 2-4th grade by NYHA) but didn't fulfill any of the excluding criteria (Age < 18 y/o, refusal of participating, oncological disease, connective tissue disease, any condition that will stop them from participating in the 6MWT), had signed the informed consent for undergoing the CT-test for the accession of muscle-tissue density.

The CT test was made with a 16-slide GE machine. The area of examination was the quadriceps at 6 cm above the patella. The tissue density was made by an imaging diagnostic specialist, the evaluations were through the Hounsfield units scale. We considered values below 35 HU as "reduced muscle tissue density".

Table 1. CT HU Density values in different tissue:

Material	Hounsfield Unit
Air	-1000
Lung	- 500 to - 200
Fat	- 200 to - 50
Water	0
Blood	25
Muscle	25 to 40
Bone	200 to 1000

Fig. 2. CT image of muscle changes with age.



From the group, most of the patients were with NYHA Class III HF, followed by those in class IV, and fewer patients were with NYHA Class II HF. In all patients, we tested muscle tissue density, and all of them did 6MWT(m). The group was split by sex. The middle age of the patients in the group was 73 ± 9 years.

Age is an independent factor for sarcopenia. In this sense, the evaluation of muscle tissue density in patients with HF in old age makes the evaluation of these patients more precise. While weight loss is related to cachexia, it is not always related to sarcopenia (the old-age-related loss of muscle mass and force) because the reduction in muscle mass can be masked by a proportional increase in adipose tissue. This can hinder the clinical diagnosis of sarcopenia, and that is why proper imaging techniques are required for accessing skeletal muscle tissue density. Methods like DEXA, CT, MRI can be used for evaluating skeletal muscle mass and density. From a clinical point of view, it is almost impossible to draw a line between sarcopenia and cachexia-related muscle waste in the end stages of HF. It should be mentioned that skeletal muscle tissue loss starts earlier than the loss of adipose tissue in the progression of H.F. Older patients with HF can develop sarcopenia before the HF-induced cachexia starts.

Table 2. Characteristics of the group with tested muscle tissue thickness:

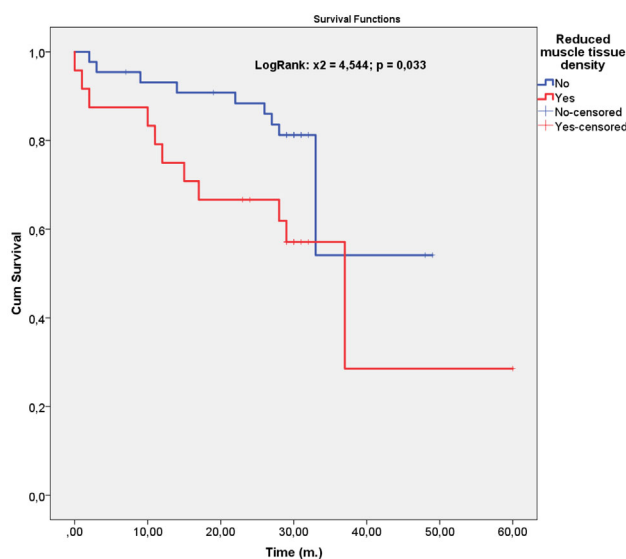
N = 70	
Age:	73 ± 9
Male (%):	36 (51, 4%)
6MWT(m):	198 ± 138
6MWT <300m(%):	53 (75, 7%)
Elevated CRP:	19 (30%)
Reduced muscle tissue (%)	24 (34, 4%)
NYHA 2(%):	2 (25%)
NYHA 3(%):	20 (35, 7%)
NYHA 4(%):	2 (33,3&)

Our analysis shows that 34.3% of the group was with reduced skeletal muscle tissue density.

According to the trials, 10-15% of HF patients develop cardiac cachexia - a condition characterized by loss of body weight due to loss of skeletal muscle and adipose tissues. Patients with severe HF develop many histological anomalies in their skeletal muscle - "cardiac skeletal myopathy".

We analyzed the survival rate in the group with reduced muscle density compared to the group without. (Fig. 3)

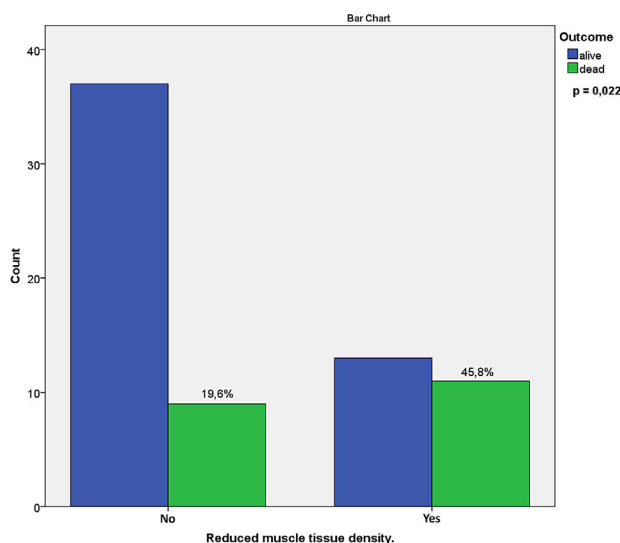
Fig. 3. Survival rate in both groups of patients with HF, with and without reduced skeletal muscle tissue density



We found out that there is a significant difference in the survival rate of both groups in favor of the group without sarcopenia.

We continued our analysis of the death rate in the same groups (Fig. 4).

Fig. 4. Death rate in both groups (HF with or without sarcopenia)



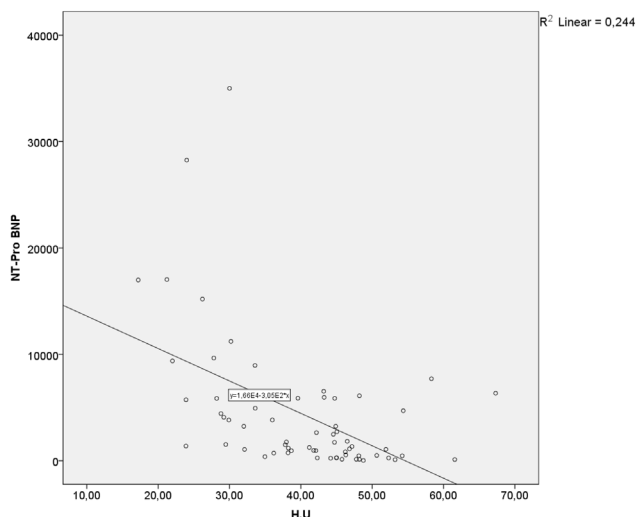
The statistics show that patients with muscle tissue density below 35 HU had a statistically significant higher death rate compare to those without sarcopenia.

Cardiac cachexia has a dramatically progressive impact on patients with HF, with 18 month-to-death probability of 50%. This condition worsens the functional capacity of patients with HF more than is expected, judging only from the evaluation of cardiac dysfunction.

The results of our research are similar with the conclusions from the trial “Comparison of Cachexia and Sarcopenia in men with CHF: Results from trials regarding HF worsening co-morbidities (SICA-HF)”. Emami A, et al. found that loss of skeletal muscle with or without body weight loss has a higher impact on functional capacity and quality of life among man with CHF. [9]

Our further research proves a strong correlative link between sarcopenia and NT-proBNP levels. (Fig. 5)

Fig. 5. Correlation link between NT-proBNP and reduced muscle tissue density



This result shows that we should be careful with patients with elevated NT-proBNP, which is not only a marker for HF, but can also be a signal for probable undergoing sarcopenia.

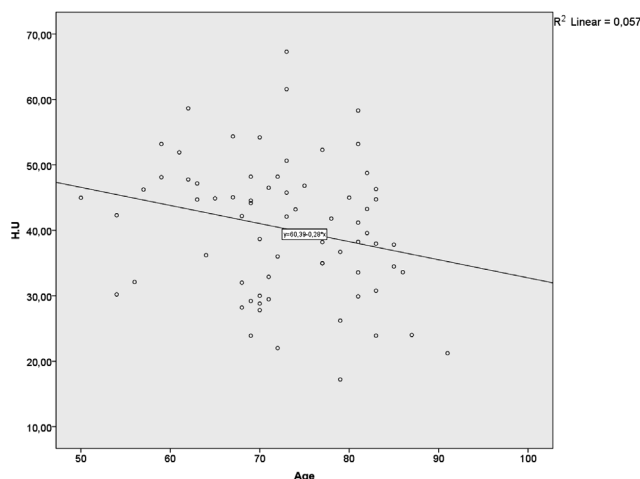
Although sarcopenia is a condition mostly dependent on age, its progression can be accelerated by the simultaneous development of other diseases, including HF. The reality is that sarcopenia affects around 20% of older-aged people with HF, which is more than the frequency of the condition in same-aged people without H.F. Older patients with HF and sarcopenia show lower physical capacity than those with HF and preserved muscle mass and function.

This result shows that acknowledging sarcopenia in the context of HF and implementing ad hoc therapeutic strategies can help improve the functional capacity of the patients before the HF reaches its later stages.

We also concluded that there is a strong correlation

between skeletal muscle tissue thickness and the age of the HF patients in the observed group. (Fig. 6) HF and age are synergetic factors that impact muscle tissue density. That is why systematic physical training should have a positive effect on patients and even postpone the outcomes of sarcopenia in all patients with HF.

Fig. 6. Correlation between levels of sarcopenia and age



Parallel presence of sarcopenia and HF is often and is probably a result of their common pathophysiological pathways such as altered intake and absorption of nutrients, inflammatory processes, metabolic and autonomic disturbances. These combined processes lead to ultrastructural muscle anomalies, changes in mitochondrial structure and function, increased oxidative stress and change in the distribution of muscle fibers, which leads at the end to reduced physical capacity and muscle strength.

CONCLUSION:

In our study, sarcopenia proved to be a significant factor in relation to mortality and survival rates of patients with diagnosed HF of all types. Although the group of patients was small, there is a statistical significance and the results of this work point one more direction in treating HF and improving the quality of life of these patients. This field of HF and cardiology has many unknowns at this time. Further studies can give many opportunities in the pathophysiological, diagnostic and therapeutic specter of the disease.

Abbreviations:

- CHF** - Chronic Heart Failure,
- HF** - Heart failure,
- CKD** - Chronic Kidney Disease,
- NSAID** - Non-steroid anti-inflammatory drugs,
- ACE-I** - Angiotensin Converting Enzyme Inhibitors,
- TNF-α** - Tumor Necrosis Factor Alpha,
- IL** - Interleukin,
- LPS** - lipopolysaccharide,
- CRP** - C-reactive protein,

IGFI - insulin-like growth factor – I,
TGF-β1 - tissue growth factor-beta one,
UPS - Ubiquitin-proteasome system,
ARBs - Angiotensin Receptor Blockers,
NO - Nitric Oxide,
MOTR - Mammalian Rapamycin Target,
ROS - Reactive Oxygen Species,

SOD - superoxydismutaza,
CT - Computer Tomography,
NYHA - New York Heart Association,
6MWT - 6 Minute Walk Test,
HU - Hounsfield Units,
DEXA - Dual Energy X-ray Absorptiometry.

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