

# SARCUS2

## Acute sarcopenia in hospitalized elderly - assessment through ultrasound

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# Acute sarcopenia in hospitalized elderly: assessment through ultrasound

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## Highlights

Sarcopenia is known as a decline in muscle function and muscle mass. It is often seen in increasing age in otherwise healthy individuals and also in those with multimorbidity. Moreover, recent studies highlight that sarcopenia can establish rapidly; this is named acute sarcopenia. In this condition acute illnesses, stressors or hospitalisation lead to a decrease in muscle mass and function because the acute stress reaction.

Traditionally, muscle mass – a part of the concept of sarcopenia – is measured by computed tomography (CT) or dual-energy X-ray absorptiometry (DEXA) scan. These devices are not always easily available in clinical practice and cannot be used bedside. An innovation in sarcopenia is the assessment of muscle mass and quality with ultrasound. Because this device is much more available and applicable in all patients, diagnosis of acute sarcopenia would be much easier with ultrasound. Moreover, if other factors that contribute to accelerated decline in muscle mass and function can be determinated, we can screen for acute sarcopenia in those individuals and hopefully reverse this mechanism.

This is the first multicenter study that will investigate the role of acute illness on sarcopenia during hospitalisation, assessed through ultrasound.

## Abstract

Sarcopenia is a geriatric syndrome defined as progressive and generalized age-related muscle loss with decline in muscle mass and muscle function (either strength or performance). It is closely related to adverse outcomes such as frailty, reduced quality of life, increased risk of falling, more frequent hospitalisations and higher mortality. Acute sarcopenia is the decline of muscle mass and function following acute disease or hospitalisation, sufficiently to meet the criteria of sarcopenia.

Objectives: To assess the effect of hospitalisation and acute illness on muscle mass and function, and to assess which other factors contribute to the development of acute sarcopenia.

Study design and main outcome measures: This study is a prospective multicenter observational study. Patients admitted to acute geriatric wards of different European centers and hospitalised for at least 5 days will be included. Measurements of muscle mass will be performed via ultrasound. Measurements of muscle function will be done by hand grip strength using Jamar dynamometer and by gait speed using the 4-meter walking test, when feasible. Other parameters will be measured via file study, laboratory investigations or validated questionnaires. Activity levels during hospitalisation will be measured through pedometers.

Anticipated results: Decline of muscle mass and muscle characteristics secondary to hospitalisation. We also expect an association with reasons of hospitalisation, pre-existing conditions, laboratory results and nutritional status prior to hospitalisation on the decline in muscle parameters.

Conclusions: This study seeks to gain knowledge of the development of acute sarcopenia and its contributing factors.

## Keywords

Acute sarcopenia, assessment, ultrasound, older people, skeletal muscle

## Clinical trial registration number

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## Abbreviations

CT, Computed Tomography; DEXA, Dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; BIA, bio-impedance analysis; MRI, magnetic resonance imaging; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRP, C-reactive protein; 25-OH-vitamin D, 25-hydroxyvitamin D; MNA-SF, Mini-Nutritional Assessment – Short Form; GLIM, Global Leadership Initiative on Malnutrition; PASE, Physical Activity Scale of the Elderly; SDPAR, Seven Day Physical Activity Recall; NMES, Neuromuscular electrical stimulation; CRM, Calorie Restriction Mimetics; EM, Exercise Mimetics.

## 1. Introduction

Sarcopenia is a well-known concept in geriatric medicine, although the definition has changed somewhat in recent years. Currently, it is defined by the second meeting of the European Working Group on Sarcopenia in Older People (EWGSOP) as a muscle disease (muscle failure), with low muscle strength as principal determinant [1].

In a review report from the International Sarcopenia Initiative, the prevalence of sarcopenia was reported according to care setting. There was a prevalence of 1-29% in community-dwelling older people, 10% in older patients in acute hospital care and 14-33% in older residents in long-term care [2]. The variability of prevalence is mostly due to the difference in assessment methods and cut-off points used. Screening for sarcopenia is very relevant in all these settings because it is correlated with mortality, functional decline, a higher rate of falls and a higher incidence of hospitalization and institutionalization [3].

A hospitalization poses an extra risk factor for older adults in terms of physical decline. Bed rest has a negative effect on muscle mass and muscle function [4-6], more pronounced in older people than in young individuals [7]. Acute illness and/or acute stress can lead to reduced muscle mass and function because of hypercortisolism and increased cortisol/dihydroepiandrosteron ratio [8], oxidative stress and inflammation processes [9, 10]. Although some data exist on acute muscle changes [6, 7, 11, 12], this concept of an acute component of sarcopenia was only first mentioned in 2016 [13].

Acute sarcopenia, secondary to an acute stressful event followed by hospitalisation, might not always recover completely and may lead to development of chronic sarcopenia [6]. Patients who have already met the criteria of sarcopenia may also develop an acute-on-chronic sarcopenia syndrome [8]. Furthermore, sarcopenia is associated with an increased length of hospital stay [14, 15], which can create a negative health spiral.

In order to prevent sarcopenia, diagnosis is paramount. There are different methods to diagnose sarcopenia [16]. Cut-off points are available for bio-impedance analysis (BIA) and dual X-ray absorptiometry (DEXA) but both lack qualitative data on muscle. Computed tomography (CT) and magnetic resonance imaging (MRI) provide both qualitative and quantitative data [16, 17], but lack cut-off points and are usually not feasible in daily practice. Ultrasound can also offer an objective and standardized measure of muscle quantity and quality, and is suitable for use on an acute ward since it is easy to perform, cheap, reproducible and can be used bedside. Previous reviews concluded that ultrasound technique is valid for measuring muscle size compared with measurement instruments such as CT and MRI [18]. Although standardization for ultrasound muscle mass measurements in older adults have been a major problem, recent efforts have tried to nullify this problem [19].

### 1.1. Objective

The aim of this study is to investigate the effect of hospitalisation due to acute illness on muscle mass characteristics, assessed in older adults through ultrasound. The primary endpoint is the change of characteristics of muscle mass in function of time since admission. The secondary endpoint of the study is to identify health related parameters associated with the development of acute sarcopenia. Relevant determinants of the evolution of muscle

mass and muscle strength since admission (reason of hospitalisation, comorbidities and laboratory data) will therefore also be investigated.

## **1.2. Hypothesis**

Hospitalisation and acute illnesses will negatively affect both muscle mass and muscle function and will hereby contribute to the development of acute sarcopenia. We hypothesize that hospitalisation due to an elevated degree of inflammation will lead to more severe decrease of muscle mass and muscle function than hospitalisation due to non-inflammatory reasons. Furthermore, certain pre-existing conditions are supposed to increase the risk of acute sarcopenia.

## **2. Methods**

### **2.1. Study design**

A prospective, multicenter, international observational study will be conducted. The study is designed to determine the effect of hospitalisation due to acute illness on the changes in muscle mass and muscle function. The secondary endpoint of the study is to identify health related parameters associated with the development of acute sarcopenia.

### **2.2. Subjects**

#### **2.2.1. Inclusion criteria**

Patients admitted between the 1<sup>st</sup> of November 2018 until the 31<sup>th</sup> of October 2019 will be eligible for inclusion. Included wards for admission are: internal medicine, acute geriatrics, orthogeriatrics and rehabilitation. Age limit will be set on 65 years and older.

#### **2.2.2. Exclusion criteria**

Patients on dialysis will be excluded because of possible metabolic features. Individuals with paresis of the lower limbs or hemiparesis due to a stroke will be excluded because of neurological involvement that can influence the results. Hypo- or hyperthyroid patients will be excluded because of the role of thyroid hormones in muscle homeostasis. Pitting oedema of the legs (due to heart failure, anasarca oedema, renal failure or liver cirrhosis) or severely dehydrated patients will be excluded because fluid shifts could influence the ultrasound measurement results. Because of possible previous changes in muscle mass, architecture and function, patients with systemic connective tissue disorders, myositis, calcification and ossification of muscle, systemic atrophies primarily affecting the central nervous system and demyelinating diseases of the central nervous system will be excluded. Patients using chronic oral corticosteroids will be excluded.

#### **2.2.3. Settings and locations**

The study will be a multicenter study held in different university and tertiary teaching hospitals throughout Europe.

## 2.3. Measurements

### 2.3.1. Patient characteristics

Date of birth, gender, height and weight will be registered. If the patient is bedridden, weight can be measured through either weight chairs or weight measuring lifts. Height will be estimated using the ulna length or knee height [20]. Date of admission and discharge will be noted. The home care setting of the patient will be registered. The main reason of hospital admission will be registered.

Comorbidities on admission will be registered through the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [21]. The CIRS-G was designed to estimate the survival of elderly persons, assessing disease severity using a score from 0 to 4 in 14 different categories of organ systems: cardiac, vascular, hematological, respiratory, ophthalmological and otorhinolaryngological, upper gastro-intestinal, lower gastro-intestinal, hepatic and pancreatic, renal, genito-urinary, musculoskeletal and tegumental, neurological, endocrine/metabolic/breast and psychiatric [22]. Score '0' stands for 'no problem affecting that system', score '1' stands for 'current mild problem or past significant problem', score '2' stands for 'moderate disability or morbidity', score '3' stands for 'severe problem' and score '4' stands for 'extremely severe problem'.

Laboratory values that will be checked are either nutritional through albumin and prealbumin, inflammatory through C-reactive protein (CRP) and white blood cell count, and the measurement of 25-hydroxyvitamin D (25-OH-vitamin D). Blood samples will be collected on day of admission. Laboratory values that are not expected to fluctuate strongly (albumin, pre-albumin, 25-OH-vitamin D) will be taken within the first 5 days of admission.

### 2.3.2. Muscle mass

In order to obtain reliable and consistent measurements, all ultrasonography will be done by an ultrasonographist that is trained to perform the measurements proposed. For the measurements, a linear probe of 5 cm width will be used. Frequency of the beam will be set on 12 MHz.

Patients should not have had any physical exercise in the 30 minutes before the measurement. Muscles should be completely relaxed and patients should be placed in the supine position, with hips in neutral position and knees fully extended. The dominant leg will be taken for the measurements. To calculate the relative muscle thickness values, the total length of muscle will be noted.

Ultrasonographic data of the four bellies of the quadriceps muscle (rectus femoris, vastus lateralis, vastus medialis, vastus intermedius) will be taken. Measuring points will be specified according to the propositions of the SARCUS-working group [19]. Muscle thickness, fascicle length, pennation angle, muscle cross-sectional area and echo-intensity of all muscles listed will be taken.

The first measurement will be taken as early as possible within 48 hours after admission at the latest. Follow-up measurements will be taken according to the type of ward the patient is admitted to. For patients that are expected to be hospitalized for a limited time (<5 days), the follow-up measurement will be done 3 days after initial measurement. For patients that are expected to be hospitalized for a longer time (>7 days), measurements will be repeated 7

days after initial measurement, to be repeated after another 7 days as long as the patient is hospitalized.

### **2.3.3. Muscle strength and function**

Muscle strength will be measured through hand grip strength using a Jamar dynamometer, using the Southampton protocol [23]. The first measurement will be taken as early as possible within 48 hours after admission at the latest. Follow-up measurements will be taken according to the type of ward the patient is admitted to. For patients that are expected to be hospitalized for a limited time (<5 days), the follow-up measurement will be done 3 days after initial measurement. For patients that are expected to be hospitalized for a longer time (>7 days), measurements will be repeated 7 days after initial measurement, to be repeated after another 7 days as long as the patient is hospitalized. Measurement will be done directly after the ultrasonographic assessment. If feasible, muscle function will be measured through gait speed, using the 4-meter walking test at usual gait speed [24]. In case of those bedridden, gait speed will not be measured.

### **2.3.4. In-hospital activity**

Registration of activity level during hospitalisation will be performed by means of pedometers in those centers that have access to these devices. Both amount of steps and step length will be noted, and total walked distance per day can hereby be calculated.

### **2.3.5. Nutritional status**

Nutritional state of the patient will be registered through the Mini-Nutritional Assessment – Short Form (MNA-SF) [25]. For diagnosis of malnutrition, the new Global Leadership Initiative on Malnutrition (GLIM)-criteria will be used [26].

### **2.3.6. Questionnaires**

The SARC-F [27] and FRAIL-scale [28] will be completed as routine screening questionnaires for sarcopenia and frailty, respectively. The SAR-QOL questionnaire will be used to evaluate the self-reported quality of life [29].

## **2.4. Statistical analysis**

Databases will be kept up in a Microsoft Access database.

Statistical analysis will be done by using SPSS Statistics version 24. Descriptive analyses will be used for determining the clinical and demographic characteristics. A Kolmogorov-Smirnov test will be used to verify the normal distribution of the different variables. Further statistical analyses will be performed by Chi Square test, Fisher exact, Mann-Whitney U test or Fisher exact test, depending on the distribution and the nature of the variables analysed. P-values of  $\leq 0.05$  will be considered statistically significant.

## **2.5. Ethics**

We will comply with both international and country specific guidelines concerning research ethics. We will also adhere to the World Medical Association Declaration of Helsinki. A written information flyer will be given to all patients and/or their family, and a written informed consent will be registered in the medical file. In patients with cognitive disorders, informed consent will be taken from the family or the main representative (proxy signature). The local

ethical committee agreement of all participating study sites will be obtained before the start of the study.

### 3. Discussion

This protocol has been designed to check whether acute illnesses or stressors followed by hospitalisation will promote the development of acute sarcopenia. This is a study protocol, and at this point no data are already available.

Although there are very few studies about the existence of acute sarcopenia, we hypothesize a relation between acute illnesses and acute sarcopenia [8]. We also hope to foresee health related parameters playing a crucial role in the accelerated development of sarcopenia, such as poor nutritional status before hospitalisation, acute inflammation and having a frail or sarcopenic status before the acute event. Certain pre-existing diseases are also believed to have an effect in worsening muscle parameters in acute illness or bedrest. It is important to identify risk factors for acute sarcopenia, so that strategies can be undertaken to prevent or at least delay the development of acute sarcopenia. Previous studies showed reduced intake of protein, reduced physical activity, inflammation, oxidative stress and low vitamin D as contributing factors to the development of (chronic) sarcopenia [9, 10, 30-32]. For acute sarcopenia, proposed risk factors include acute inflammation, reduced mobility, delirium, sleep disturbances, cognitive impairment, psychological stress and malnutrition [33-37].

A negative effect of bed rest on muscle mass has been already reported, and this effect is greater in older patients [7]. Also hypercortisolemia, as seen in acute stress and inflammatory conditions, was shown to decrease muscle mass in a study in which young adults were given hydrocortisone and bed rest [30]. Because of very fluctuating cortisol levels during the day, we chose not to measure cortisol in our study patients routinely.

Activity levels before the acute stressor occurrence, and then during hospitalisation could also be an influencing factor for acute sarcopenia. Determining activity prior to hospitalisation is however difficult. Possible tools are questionnaires like the Physical Activity Scale of the Elderly (PASE) [38] or the Seven Day Physical Activity Recall (SDPAR) [39], but those questionnaires are rather extensive and time-consuming. It could be a suggestion for further studies to examine the effect of activity pre-hospitalisation on acute sarcopenia. Activity levels during hospitalisation will be measured by use of pedometers in patients who are not bed- or chair bound.

Nutritional status at admission will be noted via the MNA-SF questionnaire [25], complementary with selected laboratory values. Although aware that malnutrition or starvation during hospitalisation will probably play an important role in development of acute sarcopenia, we chose not to register the actual nutritional intake in hospital with food record charts, because such measurements are very much observer-dependent and hereby very prone to inaccuracy.

The most important advantage of our study is that muscle mass will be measured via ultrasound, which is a relatively new way of sarcopenia screening and assessment [18, 40]. It is much more available than bio-impedance analysis or DEXA, and with less side effects than CT. It can easily be performed on a daily basis in all patients at risk for sarcopenia.

Other strengths of this study are the size of the study population (due to the multicenter setting), the comprehensiveness of assessment and the frequent, regular follow-up measurements.

There are some limitations to the study. Food intake during hospitalization will not be measured. Although nutritional intake is an important factor in retaining muscle mass, it is very difficult to correctly assess caloric and protein intake in acute patients. Also, no good measure for physical activation prior to hospitalisation is included in this research, as making a correct assessment of total exercise time and level through post-hoc recollection is often biased.

Once risk factors of acute sarcopenia are identified, we suggest to screen in those individuals in the first instance, and to pay attention to available prevention and treatment strategies. First of these strategies are physical activity interventions, with early mobilisation and intensive physical activity during hospitalisation [41]. Especially resistance exercise training and moderate aerobic exercises have been shown beneficial in improving muscle mass and function [42]. Furthermore, some nutritional interventions like protein supplementation are believed to help to prevent loss of muscle mass [43]. Especially leucine amino acid intake would be important [44]. Other interventions are still more controversial. Neuromuscular electrical stimulation (NMES) is described to prevent reductions in muscle fibre cross-sectional area [45]. This technique is however not very useful for prevention of total body skeletal muscle loss. Pharmacological interventions have been suggested for treatment of established sarcopenia, like Calorie Restriction Mimetics (CRM) and Exercise Mimetics (EM) under the form of phytochemicals [46]. Also recombinant growth hormone, testosterone supplementation, dihydroepiandrosterone and myostatine have been trialled with variable results [47-49][50]. More studies are needed to establish better pharmacological therapies to prevent or treat (acute) sarcopenia.

## 4. Conclusions

This protocol has been designed to evaluate the effect of acute illnesses followed by hospitalisation on the development of acute sarcopenia. The study is set up as a prospective observational study in which muscle mass will be measured through ultrasound assessment of the 4 bellies of the quadriceps muscle. Through the concomitant screening of other parameters as described above, their contribution to the decline in muscle mass and function in acute sarcopenia will be evaluated. When we better understand the process of development of acute sarcopenia, it might be possible to make targeted interventions for prevention and treatment of the individuals at risk.

## Contributors

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## **Declaration of interest**

None of the authors have declared any conflict of interest relating to this research.

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## Appendix

**Table 1:** Inclusion and exclusion criteria for patient participation

Inclusion criteria	Exclusion criteria
Admitted from 01/11/2018 – 31/10/2019	Dialysis
65 years or older	Previous/actual stroke
	Actual hypo- or hyperthyroidism.
	Oedema of the lower limbs
	Severely dehydration
	Systemic connective tissue disorders <ul style="list-style-type: none"> <li>• Polyarteritis nodosa and related conditions</li> <li>• Other necrotizing vasculopathies</li> <li>• Systemic lupus erythematosus</li> <li>• Dermatopolymyositis</li> <li>• Systemic sclerosis – scleroderma</li> <li>• Other systemic involvement of connective tissue</li> <li>• Systemic disorders of connective tissue in diseases classified elsewhere</li> </ul>
	Myositis
	Calcification and ossification of muscle
	Systemic atrophies primarily affecting the central nervous system <ul style="list-style-type: none"> <li>• Huntington's disease</li> <li>• Hereditary ataxia</li> <li>• Spinal muscular atrophy and related syndromes</li> <li>• Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere</li> <li>• Postpolio syndrome</li> </ul>
	Demyelinating diseases of the central nervous system <ul style="list-style-type: none"> <li>• Multiple sclerosis</li> <li>• Other acute disseminated demyelination</li> <li>• Other demyelinating diseases of central nervous system</li> </ul>
	The chronic use of oral corticosteroids