Sarcopenia in acute care patients: Protocol for the European Collaboration of Geriatric Surveys: Sarcopenia 9+ EAMA project

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ABBREVIATIONS

BMI: Body mass index

CKD-epi: Chronic Kidney Disease Epidemiology collaboration

COPD: Chronic obstructive pulmonary disease

EAMA: European Academy for Medicine of Ageing

EuGMS: European Union Geriatric Medicine Society

EWGSOP: European Working Group on Sarcopenia in Older People

EWGSOP2: Revised European Consensus on definition and diagnosis

GLISTEN: Gruppo Lavoro Italiano Sarcopenia, Trattamento E Nutrizione

IQR: Interquartile range

MNA-SF: Mini-Nutritional assessment-Short form

SD: Standard deviation

SIG: Special Interest Group on Sarcopenia

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology Statement.

BACKGROUND

Sarcopenia is a disease(1) characterized by progressive and generalized loss of skeletal muscle mass and strength, and is related to worse clinical outcomes, physical impairment(2), and mortality(3) in all healthcare settings(4). This nutrition-related didsease(5) is reversible and can be effectively counteracted by exercise and nutritional support(6)(7)(8)(9).

The prevalence of sarcopenia varies widely depending on the criteria, methods, and cut-off points used for its assessment(10)(11). Although the European Working Group on Sarcopenia in Older People (EWGSOP) recommended assessing sarcopenia in geriatric patients in all care settings(4)(12), few studies addressing hospitalized older patients have been carried out, mainly due to the characteristics of acute healthcare settings and their in-patients(13)(14)(15)(16) and because the criteria used are difficult to carry out there. Therefore, this condition remains under-recognized in the setting where this disease(1) is likely to be more present(13)(14).

Sarcopenia is expected to be a major healthcare problem in the upcoming years in Europe(17), so, in response to this claim for Public Health Action, the European Union Geriatric Medicine Society founded the Special Interest Group (SIG) on sarcopenia that has taken the lead of bridging the gaps between clinical and research(18) in sarcopenia field(18), in line with the Conference on Frailty and Sarcopenia Research Task Force(7), and the World Health Organization's strategies to promote Optimal Aging(19). This goal of SIG on sarcopenia by EuGMS is being carried out by promotion of collaboration among International scientific societies and institutions; they have recently launched the Revised European consensus on definition and diagnosis (EWGSOP2)(4), the SARCUS project on ultrasound for sarcopenia

assessment in European countries(20)(21), and the first International Registry of patients with sarcopenia(22).

The new goal, assumed by the SIG on Sarcopenia is to assess sarcopenia in acute healthcare settings across European countries. This challenging project has been developed involving The European Academy for Medicine of Ageing (EAMA) is a postdoctoral fellowship on behalf of the EuGMS formed by European specialists in Geriatric Medicine focused on improving networking, establishing specific fields of interest, and providing an opportunity for lifelong learning(23). The Sarcopenia 9+ EAMA project working group has assumed the goals stablished by SIG on Sarcopenia by EuGMS and is focused on sarcopenia in acute healthcare settings across European countries.

Our study aims to provide an overview of sarcopenia assessment in hospitalized older patients across 9 European countries and has 5 objectives:

1. To determine prevalence of sarcopenia among hospitalized patients in Europe.
2. To determine incidence of sarcopenia during the hospital stay.
3. To identify risk factors for the development of sarcopenia at the time of admission and during hospitalization (i.e. malnutrition as defined by the Global Leadership initiative on Malnutrition).
4. To assess sarcopenia as a risk factor for clinical adverse outcomes during hospitalization (hospital-acquired infections, falls, delirium, longer length-of-stay, disability, and mortality).
5. To assess sarcopenia as a risk factor for clinical adverse outcomes post-discharge (institutionalization, hospitalizations, falls, disability, and mortality) at 3- and 12-month follow-up.

METHODS

Design: Longitudinal, prospective, observational multicenter study in consecutive hospitalized patients in 9 European countries [Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Spain, and United Kingdom]. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement will be followed(24). No major changes to methods or eligibility criteria after study commencement are planned.

Settings: Acute-care geriatric units. The description of the 9 settings involved in data collection has been stated in the affiliation section.

Participants: Patients aged 70 years and older who are admitted to the acute care geriatric units will be included. This may include acute medical conditions or chronic disease decompensation; patients are eligible for referral to acute geriatric units due to medical diseases, such us urinary tract infections, respiratory tract infections, pneumonia, coronary heart diseases, atrial fibrillation, congestive heart failure, stroke, delirium, electrolyte disturbances, kidney disease, cancer, etc... Exclusion criteria: Length of stay less than 24 h expected, inability to perform hand-grip, hip or lower limbs fractures, amputations, terminally ill patients admitted for palliative care, and unwillingness to take part in the study.

Main outcome measure: 1) Prevalence of sarcopenia at admission (± 48h). A prevalent case of sarcopenia will be considered if a patient fulfills the EWGSOP2 at admission; 2) Incidence of sarcopenia between admission and discharge (± 24h). A incident case of sarcopenia will be considered if a patient that do not fulfill EWGSOP2 diagnostic criteria at admission, fulfills the diagnostic criteria at discharge (diagnosis will be considered as a dichotomous variable -yes/no-); 3) Risk factors involved in the

development of sarcopenia during hospitalization; 4) Clinical adverse outcomes related to sarcopenia (incidence of hospital-acquired infections, falls, delirium, length-of-stay, disability, and mortality); 5) Clinical adverse outcomes post-discharge (institutionalization, hospital readmissions, falls, disability, and mortality) at 3- and 12-month follow-up.

Variables of sarcopenia (Table 1). SARC-F questionnaire will be administered for sarcopenia screening(25)(26): a score ≥4 (from a maximum of 10) will be considered as predictive of sarcopenia. EWGSOP2 criteria will be followed to determine the diagnosis of sarcopenia, considered as a dichotomous variable -yes/no- in presence of low grip strenght + low muscle mass + low gait speed for severity grading(4). Muscle strength will be measured by isometric handgrip dynamometry (hand-held dynamometer model JAMAR©] following standardized methods(27)(28); the corresponding cut-off points recommended by EWGSOP2 will be used (27 Kg en men and <16 in women)(27). Muscle mass will be assessed by calf circumference, considering a cut-off point of <31cm(27)(29). Gait speed will be measured by 4-m walk test(27)(30), where a cut-off point of 0.8m/s will be used(27)(31). Gait speed will be considered 0 m/s in bedridden patients unable to stand or in those unable to walk in safety conditions(13)(14)(32)(33).

Other variables: Age, sex, comorbidity (Charlson index), functional status by instrumental (Lawton index)(34) and basic (Barthel index)(35) activities of daily living, medical conditions, and diagnosis at admission will be recorded. The Barthel index will be used to assess functional status one week before hospital admission (by clinical interview with patients and confirmed by caregivers, medical records, and general practitioner as appropriate), at admission, and at discharge(36)(37). Functional changes, calculated by subtracting the Barthel index at admission from the Barthel index at

discharge, will be recorded(37). Drugs will be recorded by the Anatomical Therapeutic Chemical (ATC) Classification System. Marital status living conditions, dependent on carers, years of education, level of pain (11-point pain intensity numerical rating scale, PI-NRS-)(38)(39), and level of usual physical activity by the Rapid Assessment of Physical Activity will be also recorded. Variables related to hospital admissions (time of admission and discharge), and number of hospitalizations during the last and previous 3 months) will also be recorded.

Nutritional assessment: The Global Leadership Initiative on Malnutrition (GLIM) criteria will be followed to diagnose malnutrition(8)(40). All in-patients will be screened for risk of malnutrition at admission by the Mini-Nutritional Assessment Short-Form (MNA-SF)(41); days of fasting, defined as the non-consumption of at least two main meals, will also be recorded. Body weight will be measured to the nearest 0.1Kg; height will be measured in all patients able to stand in safety conditions, otherwise a knee-height equation(42) will be applied. **Cognitive status** will be assessed by Mini-Mental State Examination, Geriatric Depression scale (GDS15), as well as presence of delirium by the CAM. **Frailty** will be assessed by the FRAIL scale(43) and frailty phenotype(44).

Biochemical values for total proteins, albumin, high (LDLc) and low-density lipoproteins cholesterol (HDLc), total cholesterol, triglycerides, apoB cholesterol, homocysteine-related markers (folic acid and B12 vitamin), vitamin D, glycosylate haemoglobin (Hb1C), iron profile (serum iron, transferring saturation, and ferritin), thyroid-stimulating hormone, electrolytes (sodium, potassium), renal profile [creatinine, urea, and glomerular filtration rate from the Chronic Kidney Disease Epidemiology Collaboration (CKD-epi)], hemoglobin, erythrocyte sedimentation rate test, albumin, and C-reactive protein will be obtained.

Procedure (Table 2). Patients will receive a comprehensive geriatric assessment by an interdisciplinary team and a care plan for their specific needs, as part of the usual care in acute wards at admission. Tests for the diagnosis of sarcopenia will be performed within 48h of hospital admission, and again at discharge (± 24h) by the interdisciplinary team involved in this study. Discharge will be defined as the moment when the patient leaves the acute care hospital independently of their destination, to ensure coherence among countries in despite of the different healthcare resources (home back to Primary care, hospital-at-home scheme, care home (residential or nursing), postacute, transitional or rehabilitation care, transferred to another acute ward); all patients will be discharged according to clinical criteria as part of usual care of the unit, independently of the diagnosis of sarcopenia. Sarcopenia (outcome measure variable) will be assessed using EWGSOP 2 criteria and recorded at admission and at discharge. SARC-F questionnaire will be administered at admission and at 3- and 12- month follow-up. Blood samples will be extracted at admission by a trained member (usually a nurse) of the interdisciplinary team.

Hospital admission. Demographic data (age, date of birth, sex, marital status, living conditions, education level), administrative data (time of admission, number of previous hospital admissions in the last month and in the last 3 months), prevalent and incident medical conditions (Charlson index), diagnosis for hospital admission, hypertension assessment, medication use (Anatomical Therapeutic Chemical (ATC) Classification System, functional (Barthel index), nutritional (MNA-SF, weight, height, diagnosis of malnutrition as defined by GLIM), frailty (FRAIL and Frailty phenotype), and cognitive assessment (MMSE, GDS15, CAM), and pain (PI-NRS) will be collected within 48h of admission. **Hospital discharge.** Administrative data (time of discharge and place of discharge), medication use, weight, functional status, in-hospital adverse

outcomes (urinary and respiratory tract infections, falls, and delirium), presence of pain (PI-NRS), days of fasting and bed rest, hypertension and orthostatic hypotension assessment, and mortality will be addressed within 24h prior to hospital discharge. **Follow-up.** Administrative data (date of the follow-up, hospital re-admissions, and visits to the emergency department), SARC-F questionnaire), pain (PI-NRS), functional status (Barthel index), institutionalization, hospital readmissions, and mortality after discharge will be assessed and collected by telephone interview with the patient or caregiver or from medical records at 3-month and 12 month-follow-up.

Chronogram and dynamics (Table 3): Email will be used for communications among the working group members. All the EAMA working groups have approved the study protocol. The approval of the Ethics Committees of all settings will be requested in all centers. Field work and data collection will start as soon each partner will obtained their respective Ethics Committee approval. Each partner will collect data during 4 months or the time needed to assess approximately 100 patients; however, every team may continue collecting data until the last team has finished the field work, if they choose to do so. A minimum of 50 patients should be collected by each partner, if possible, and no upper limit will be imposed. If one of the working group members is unable to complete the field work, collaboration in other tasks will remain an option. Data collection will be recorded in an Excel spreadsheet and analysed by the groups from Belgium, Germany, Italy, Spain, Poland, and United Kingdom.

Sources of funding: No external funding is anticipated. Every member of the working will use their own human and technical resources to develop the different phases of the study. The working group may seek eventual sources of funding (ERC, ESPEN grant fellowship, Erasmus+ Teaching, National grants, Fondo Investigación en

Salud Carlos III in Spain…) depending on the results of the ongoing project in further stages.

Statistical analysis: Descriptive analysis of the sample will use percentages and frequency distributions for categorical variables, and means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables. Univariate analysis will be used to check clinical and functional characteristics of the study participants according to the diagnosis of sarcopenia as defined by EWGSOP. Categorical variables will be compared by Chi-square or Fisher exact test, as appropriate, and continuous variables by Student *t* test. Univariate and multivariate analyses will be performed for all outcomes to examine possible associations with covariables. P values <0.05 will be considered as statistically significant. Statistical analysis will be performed using STATA 15.0 software (Stata Corp.; College Station, Texas, USA).

Sample size determination: Sample size was calculated in terms of the Sarcopenia 9+ EAMA project objectives; a sample size of 369 patients randomly selected will suffice to estimate with a 95% confidence and a precision ±5 percent units, a prevalence of sarcopenia at admission considered to be around 40%. For the incidence of sarcopenia study, a sample size of 218 patients randomly selected will suffice to estimate with a 95% confidence and a precision ±5 percent units, a population percentage considered to be around 15%. It has been anticipated a replacement rate of 10%; this relatively low percentage of loss reflects the expected adherence to usual care and follow-up of patients in a geriatric acute ward and a geriatric outpatient clinic for the duration of the study. Sample size calculation was performed using GRANMO

(Calculadora de Grandària Mostral GRANMO, version 7.12. Abril 2012, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain)(45).

Ethics: National and international research ethics guidelines will be followed(46), including the Deontological Code of Ethics, Declaration of Helsinki, and Spain's confidentiality law concerning personal data (*Ley Orgánica* 15/1999, 13 December, *Protección de Datos de Carácter Personal*). Detailed, understandable oral and written information will be provided to patients and family members (see file attached, **Information file,** including and in concordance with the General Data Protection Regulation (GDPR), informed consent to participate will be signed (see file attached, **Informed consent**). The study has been approved by Parc Salut Mar, Local Ethics Committee, Barcelona (CEIm - Parc Salut Mar, ref. number. 2018/8355/I), CHU Brugmann, Brussels (CE 2019/26), Krakow University Hospital, Krakow, and Centro Hospitalar Universitario de Lisboa, Lisbon (Processo n.°596/2018), and is currently submitted and pending of approval in the rest of centers. Data will be entered are treated in accordance with the provisions of the applicable data protection law in Spain and the General Data Protection Regulation (GDPR) (EU) nº 2016/679 of the European Parliament and Council, dated the 27 April of 2016, which entered into force last 25 May 2018.

Possible points for the discussion section

This is a protocol for a study to determine the prevalence and incidence of sarcopenia, to assess the factors involved in its onset and its clinical adverse outcomes during hospitalization in acute care and post discharge in a 3 and 12-month follow-up in in Europe; no data are yet available. The overall purpose of our study and is to take a

pragmatic approach in assessing sarcopenia in clinical practice in Europe and provide insight to develop eventual therapeutic interventions.

To date, few studies have addressed sarcopenia in hospitalized patients and no data are available across Europe. Following the model of the multicentre GLISTEN study, which assessed sarcopenia in acute geriatric care settings across Italy(13)(14), our survey will assess the prevalence, incidence, risk factors, and clinical outcomes of sarcopenia in hospitalized patients in 9 European countries. One of the limitations of our study will be the assessment of sarcopenia at discharge, mainly due to three issues.

First, the status of patients at discharge depends on their evolution; therefore, discharge is not a unifying condition. For example, patients may be discharged home independently due to complete resolution of the acute process or discharged to a postacute care setting to recover functional status; some countries have very short hospital stays and as soon as the patient are stable, they are sent to other institutions for rehabilitation, others have longer length of stay and receive rehabilitation in the hospital. In order to address this methodological limitation, An additional regular point of assessment at the 7-10th **b** day of admission had been planned, but finally, the authors considered that it was difficult to be performed and added extra workload, so, it was deleted to the study protocol; further studies might be able to include this additional assessment point in those patients with an extended hospital stay. Second, although the concept of being discharged was defined to gain consistency on the definition and minimize differences due to healthcare resources, every country has different discharge procedures and the clinical criteria to discharge a patient from acute care still might differ from clinician to clinician and from country to country. Finally, the concept of "acute care units" or "institutionalization" also may differ by country, depending on

care assistance levels and the strategies of the respective national health systems across Europe.

Another potential limitation of our study is the use of anthropometric measures to assess muscle mass, which is much more practical and widely applicable than alternative measures of muscle mass. Although acknowledged by the EWGSOP to assess muscle mass, its use might be controversial(29)(47) and could open a research line for further studies using other assessment tools.

Some strengths of our study might be highlighted, and positive results are already anticipated, as an additional goal is to establish a stable European partnership on sarcopenia in order to develop further research projects and collaborations. Other aspect to be highlighted is that the study protocol includes the most important clinical adverse outcomes, such as mortality, hospitalization, institutionalization, falls, disability, and mortality.

The initial **Publication plan** is promising and additionally from the main objectives, new topics on sarcopenia field are expected to be assessed, i.e. sarcopenia and frailty as nutrition-related conditions and their relationship with malnutrition as defined by GLIM criteria, a new, unified, international definition launched by the largest enteral and parenteral societies worldwide in October 2018, and which is pending of validation(8)(40). Other novel topics to be included in the Publication plan are the relationships between sarcopenia, hypertension, and orthostatic hypotension; and the relationship between sarcopenia and delirium, whose augmented risk when sarcopenia is present at admission was also recently assessed in the GLISTEN study(50). Collaborative partnerships and external proposals for use of data will be welcome and checked by the Sarcopenia 9+ EAMA working group before approval; those proposals admitted will be included in the Publication plan of this working group.

The desired outcome is the application of emerging research in clinical practice, following the "Action-Research Philosophy"(51), in order to improve care in patients with sarcopenia. Knowledge about the incidence of sarcopenia and its onset might shed light on its staging, in order to develop eventual therapeutic strategies.

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