BMJ Open

Biomarkers for length of hospital stay, changes in muscle mass, strength and physical function in older medical patients: protocol for the Copenhagen PROTECT study—a prospective cohort study

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To cite: Kamper RS, Schultz M, Hansen SK, *et al*. Biomarkers for length of hospital stay, changes in muscle mass, strength and physical function in older medical patients: protocol for the Copenhagen PROTECT study—a prospective cohort study. *BMJ Open* 2020;**10**:e042786. doi:10.1136/bmjopen-2020-042786

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-042786).

Received 14 July 2020
Revised 08 December 2020
Accepted 11 December 2020

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ABSTRACT

Introduction Sarcopenia is generally used to describe the age-related loss of muscle mass and strength believed to play a major role in the pathogenesis of physical frailty and functional impairment that may occur with old age. The knowledge surrounding the prevalence and determinants of sarcopenia in older medical patients is scarce, and it is unknown whether specific biomarkers can predict physical deconditioning during hospitalisation. We hypothesise that a combination of clinical, functional and circulating biomarkers can serve as a risk stratification tool and can (i) identify older acutely ill medical patients at risk of prolonged hospital stays and (ii) predict changes in muscle mass, muscle strength and function during hospitalisation.

Method and analysis The Copenhagen PROTECT study is a prospective cohort study consisting of acutely ill older medical patients admitted to the acute medical ward at Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark. Assessments are performed within 24 hours of admission and include blood samples, body composition, muscle strength, physical function and questionnaires. A subgroup of patients transferred to the Geriatric Department are included in a smaller geriatric cohort and have additional assessments at discharge to evaluate the relative change in circulating biomarker concentrations, body composition, muscle strength and physical function during hospitalisation. Enrolment commenced 4 November 2019, and proceeds until August 2021.

Ethics and dissemination The study protocol has been approved by the local ethics committee of Copenhagen and Frederiksberg (H-19039214) and the Danish Data Protection Agency (P-2019-239) and all experimental procedures were performed in accordance with the Declaration of Helsinki. Findings from the project, regardless of the outcome, will be published in relevant peer-reviewed scientific journals in online (www.clinicaltrials.gov).

Trial registration number NCT04151108

Strengths and limitations of this study

- A strength of the study is the large heterogeneous population, which brings generalisability to the study results.
- The assessments of physical function applied in the study have previously been evaluated in acutely admitted older medical patients.
- Bioelectrical impedance analysis may be affected by the hydration status of the patients.
- There are no direct measurements of the physical activity levels of the patients during admission.
- The study estimates stature by knee-height measurements, as many patients are unable to stand for height measurements.

INTRODUCTION

It is well-established that human skeletal muscle function declines with ageing, and sarcopenia is generally used to describe the age-related skeletal muscle atrophy and loss of muscle strength believed to play a major role in the pathogenesis of physical frailty, loss of independence and functional impairment that may occur with old age.[1–3] Clinical sarcopenia has been defined in statistical terms assuming a lower normal limit of two SD below a mean relative appendicular muscle mass in young healthy adults.[4] The prevalence of sarcopenia is estimated at 5%–13% in 60–70 years old and 11%–50% in individuals aged 80 years or older.[5] The aetiology of sarcopenia is complex and involves neuronal, hormonal, immunological and nutritional mechanisms.[6–10] Furthermore, physical inactivity, chronic diseases, immobilisation and

hospitalisation are known to play a part in the development of sarcopenia.[6 11–13]

In 2018, approximately 45% of all hospital admissions in Denmark concerned patients aged 65 or older who had a mean length of stay (LOS) of 3.5 days.[14] Older patients are often inactive during hospitalisation spending 71%–83% of their time lying down,[15 16] and at least 35% of older patients lose independence in one basic activity of daily living as an unintended consequence of a medical illness and hospitalisation.[17] Sarcopenia may aggravate this functional decline, as patients with sarcopenia have an attenuated recovery of their functional levels 3 months following discharge.[18] From a clinical perspective, sarcopenia is associated with infectious complications, readmissions, increased need for rehabilitation following discharge, reduced quality of life, increased mortality and longer hospitalisation.[4 19]

Early mobilisation protocols have proven effective in reducing hospital-acquired disability and hospital length of stay. However, frequently reported barriers for implementation of early mobilisation include lack of staff and time to enable mobilisation of the patient.[20] With an increasing ageing population and the heterogeneousness of older individuals, the systematic identification of older individuals at risk of prolonged hospitalisation and deconditioning during hospitalisation are of outmost importance. As such, the combination of clinical, functional and circulating biomarkers may serve as risk stratification tools to identify older patients at risk of these adverse outcomes.

STUDY OBJECTIVES AND HYPOTHESES

Primary objectives and hypothesis

We aim to examine whether circulating biomarkers at admission are associated with length of hospital stay in older (≥65 years) acutely admitted medical patients and whether the combination of clinical and functional measures with these biomarkers can identify patients at risk of having a prolonged hospital stay (>96 hours). In addition, we aim to establish circulating biomarkers associated with changes in muscle mass, muscle strength and function in geriatric patients during hospitalisation. We hypothesise that a combination of clinical and functional measures with circulating biomarkers has the potential to identify older (≥65 years) acutely admitted medical patients at risk of prolonged (≥96 hours) hospital stays and physical deconditioning during hospitalisation.

Secondary objectives and hypothesis

The secondary objectives are to determine whether circulating biomarkers are associated with readmissions within 90 days of discharge, frailty, discharge to a higher level of care and all-cause mortality within 90 days of the index admission and whether the combination of clinical and functional measures with these biomarkers can identify patients at risk of readmissions, discharge to a higher level of care and all-cause mortality. We hypothesise that a combination of clinical and functional measures with circulating biomarkers has the potential to identify older (≥65 years) acutely admitted medical patients at risk of non-elective readmissions within 90 days of discharge, discharge to a higher level of care, and all-cause mortality within 90 days of the index admission.

METHODS AND ANALYSIS

Setting and intervention

The Copenhagen PROTECT study is a prospective cohort study consisting of acutely ill older medical patients admitted to the acute medical ward at Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark. A subgroup of these patients, subsequently transferred to the Geriatric Department, are also included in a smaller geriatric cohort. Enrolment commenced 4 November 2019 and will proceed until August 2021.

Eligible patients

The current study is recruiting participants during a 1.5-year period to avoid any seasonal differences in the patient population and to take into account the temporary pause in recruitment due to the COVID-19 pandemic. We aim to include a total of 1700 patients representing the PROTECT cohort, of which approximately 400 patients subsequently will be transferred to the Geriatric Department and constitute the Geriatric cohort. All patients admitted at the acute medical ward at Copenhagen University Hospital, Bispebjerg and Frederiksberg who fulfil the inclusion criteria and do not meet any exclusion criteria are eligible for the study (box 1). The hospital admission during which the patient is recruited represents the index admission. Any subsequent non-elective admissions of included patients during the study inclusion period will be interpreted as readmissions. Included patients will be followed for 90 days following discharge from index admission to investigate future readmissions and mortality.

Outcomes

The primary outcome in the PROTECT cohort is the length of hospital stay. Successive events of hospitalisation have been suggested to contribute to the development of sarcopenia, and even short periods (4–5 days) of skeletal

Box 1 Inclusion and exclusion criteria

Inclusion criteria
Equal to or over the age of 65 years.
Acutely admitted with a medical diagnosis (ie, non-surgical).
Exclusion criteria
Admitted for more than 24 hours prior to baseline assessment.
Terminal illness (expected life span of less than 6 months)
Temporary civil registration number.
Droplet or airborne infections requiring isolation.
Does not speak or read Danish.
Patients judged medically contraindicated by health personnel.
Inability to provide informed consent for participation.

Box 2 Primary and secondary outcomes in the PROTECT cohort

Primary outcome
Length of hospital stay.
Secondary outcomes
Non-elective readmissions within 90 days of discharge.
All-cause mortality within 90 days of index admission.
In-hospital mortality.
Muscle mass at admission.
Muscle strength at admission.
Muscle function at admission.
Frailty.

muscle disuse are known to induce muscle atrophy.[21 22] In 2018, the mean length of hospital stay in Denmark was 84 hours in patients aged 65 years or over.[14] while the mean LOS in the two largest local hospitals was 96 hours. As such, we have defined a prolonged hospital length of stay as an admission lasting >96 hours.

The primary outcomes in the Geriatric cohort are the relative changes in muscle mass, muscle strength and muscle function during hospitalisation. Primary and secondary outcomes for the PROTECT cohort and the Geriatric cohort are listed in boxes 2 and 3, respectively.

We have defined geriatric patients discharged to an increased level of care as (i) patients receiving increased relief in terms of walking aids or patients with an increased need for caregiver assistance or home care, (ii) patients referred to rehabilitation or 24 hours care or (iii) patients moving to a nursing home following discharge. Data on readmissions will be limited to non-elective readmissions in Region Zealand and the Capital Region of Denmark. A geriatrician will evaluate whether the readmission is related to the index admission; that is, newly emerged acute illness following the index admission, acute aggravation of disease treated during the index admission or complication to treatment during the index admission.

Assessment and randomisation

The research personnel might be unable to assess all patients, as the number of eligible patients (ie, fulfilling inclusion criteria with the absence of exclusion criteria) varies daily. Thus, to avoid selection bias, all eligible patients on the day in question are randomised using a computer-generated randomisation sequence to establish a randomised visitation sequence. Patients who wish to participate sign an informed consent and baseline measurements are performed within the first 24 hours of admission. All included patients have blood samples drawn to determine concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-10, transforming growth factor (TGF)-β1, follistatin, insulin-like growth factor (IGF)-1, growth differentiation factor (GDF)-11, GDF-15 and soluble urokinase-type plasminogen activator receptor (suPAR).

Box 3 Primary and secondary outcomes in the Geriatric cohort

Primary outcomes
Changes in muscle mass during hospitalisation.
Changes in muscle strength during hospitalisation.
Changes in muscle function during hospitalisation.
Secondary outcomes
Length of hospital stay.
Non-elective readmissions within 90 days of discharge.
All-cause mortality within 90 days of index admission.
In-hospital mortality.
Discharge to an increased level of care.
Frailty.

Handgrip strength is assessed using a digital hand-held dynamometer (Model SH1001; SAEHAN Corporation, Yangdeok-Dong, Masan, South Korea). Patients able to leave the bed sit on a chair with the elbow flexed at 90° and the wrist in a neutral position, while bedridden patients are assessed in the hospital bed with the backrest elevated. The highest value of three attempts with the dominant hand is used for analyses. Should the third trial elicit the highest value, the patient continues until a lower value is achieved. Muscle function is assessed in the 30 s sit-to-stand test, where patients are asked to stand up from a standardised chair as many times as possible with their arms folded across the chest. Only full standing positions are counted.[23 24] Patients included in the Geriatric cohort also have their habitual gait-speed assessed. The gait-speed assessment is measured over a course of 4 m and includes walking aids if they are used by the patient. Patients stand behind a starting line and are asked to start walking towards a visual goal at their habitual pace. The visual goal is placed after 5.5 m. to reduce the effect of deceleration. The fastest of the two attempts will be used for analyses and quantified as m/s.[23] The assessment of handgrip strength (kg) and habitual gait-speed have previously shown to be feasible and reliable measures in acutely older medical patients. However, the feasibility and reliability of the 30 s sit-to-stand test was moderate, as only half of the patients were able to perform the test as instructed.[23] Thus, we have included an additional nominal variable to categorise the sit-to-stand ability as either (i) able to perform the test as instructed, (ii) ability to rise using the armrest and (iii) inability to rise independently from a chair.

Bodyweight (kg) is assessed using chair scales and height (cm) is estimated with a segmometer using the knee-height measurement and age with the equations from Chumlea *et al*.[25] Body composition, including whole body phase angle, is assessed using Direct-Segmental Multi-frequency Bioelectrical Impedance Analyses (DSM-BIA) (InBody S10; Biospace, Seoul, Korea), which has previously been used in elderly acutely admitted patients with a mean LOS of 5 days.[26] Self-reported current smoking is reported as a dichotomous variable. Patients included in the Geriatric cohort are also assessed at discharge to evaluate circulating biomarker concentrations as well as changes in body composition, muscle strength and

functional performance. Tests of strength, physical function and body composition measurements are performed by trained research personnel. The presence of frailty is assessed by trained nurses associated with the study using the Canadian Study of Health and Aging Clinical Frailty Scale.[27] Patients are screened for sarcopenia using the SARC-F questionnaire,[28] while cognitive status is evaluated by the short Orientation-Memory-Concentration test.[29] The risk of malnutrition is assessed and validated using the Short Nutritional Assessment Questionnaire.[30] A flowchart showing the timeline and assessments in the two cohorts can be seen in figure 1.

Information on medical treatment is evaluated by counting all prescribed medications, including unscheduled medications, except for the following:

- Eyedrops.
- Eardrops.
- Lotions and ointments.
- Antibiotic treatment of limited duration.
- Multivitamins.
- Supplementary nutrition or tube feeding.

Medications listed two times containing the same substance are only counted once. Comorbidity is evaluated by the Charlson Comorbidity Index[31] and obtained by evaluating the type and number of International Classification of Diseases (ICD)-10 discharge diagnosis during the last 5 years of the index admission. Sepsis is defined in accordance with the Sepsis-3 criteria.[32] Data on emigration and all-cause mortality within 90 days of index admission is extracted from the Danish Civil Registration System. A summary of variables assessed by research personnel and extracted from the electronic patient system (EPIC) or the Danish Civil Registration System are listed in table 1.

Data management

Following data acquisition, all physical documents are stored in accordance with the guidelines for data management from the Danish Data Protection Agency. Electronic data are managed and stored using Research Electronic Data Capture (REDCap),[33 34] a web-based secure software platform hosted at Bispebjerg-Frederiksberg University Hospital. To ensure data quality, the REDCap database was built to ensure data integrity including real-time data validation, integrity checks and range checks for data values.

Patient and public involvement

On request, patients with measures of muscle mass, strength or function can gain insight into their values and receive advice to improve from either an exercise physiologist or a physiotherapist. Patients are not involved in the study design, recruitment or other aspects of the study.

Power calculation and statistics

To evaluate the prognostic abilities of circulating biomarkers (individually, in combination and combined with clinical and functional measures) we will use the area under the curve for receiver operating characteristics (AUROC) statistics. A reference group of 2058 patients over the age of 65 from Bispebjerg-Frederiksberg University Hospital and Herlev-Gentofte Hospital had a mean age of 78.3 years and a mean length of stay of 5.8 days during hospitalisation. In these patients, 817 (39.7%) had a prolonged length of stay, defined as a hospitalisation lasting more than 96 hours. With a sample size of 1700 and the assumption that approximately 40% of older medical patients have a prolonged hospital stay, an AUROC of 82 will have a power of 0.9 with a significance level of 0.05.

A table of summary statistics will be presented with baseline variables. Continuous variables will be summarised with the following: n (non-missing sample size), mean, SD, median, IQR and number of missing values. Categorical variables will be reported as frequency and percentages (based on non-missing sample size), and number of missing values. Data missing at random will be imputed using multiple imputation.

To evaluate whether clinical, functional and circulating biomarkers are associated with length of stay we will perform multivariate logistic regression. Patients will be grouped in either normal (<96 hours) or extended length of stay (≥96 hours) and Cox regression analysis will be used to compare differences in non-elective readmission and all-cause mortality. Patients will be followed from the date of discharge from the index admission until the end of the follow-up period, emigration, readmission, or death as appropriate. To assess the discriminative ability of biomarkers with regards to an extended length of stay and all-cause mortality, we will use the area under the curve (AUC) for receiver operating characteristics (ROC) curves. AUCs for different ROC curves will be compared using the DeLong test. The association of circulating biomarkers with changes in muscle mass, muscle strength and function in the geriatric cohort will be assessed using a multivariate linear model adjusted for the relative length of stay.

Study organisation

The study is a researcher initiated clinical study. The protocol was written by the steering committee composed of experts in geriatric medicine and acute medicine and a PhD student in basic and clinical research in musculoskeletal sciences. The committee is responsible for the design of the study, supervision of research personnel, data acquisition, communication and publication of results, approval of substudies and ensuring that future studies comply with the regulations regarding data management.

At present (July 2020), the study has included 377 patients, of which 62 are part of the geriatric cohort. Inclusion was temporarily paused due to the impact of the COVID-19 pandemic.

ETHICS AND DISSEMINATION

All procedures are being conducted according to 'Good Clinical Practice' standards, regarding initiation, monitoring and reporting. The study protocol has been

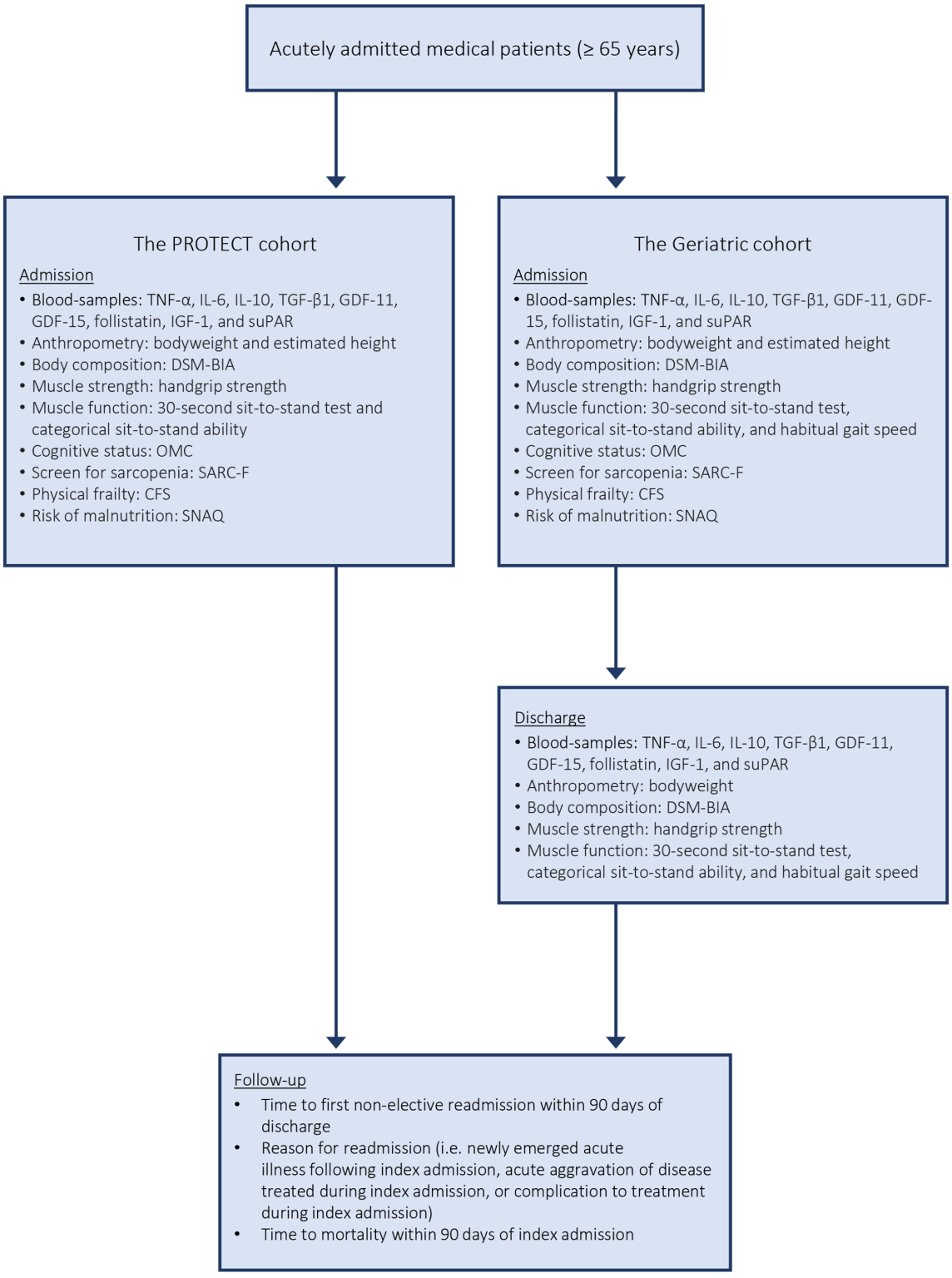

Figure 1 Timeline and assessments in the PROTECT cohort and the Geriatric cohort. CFS, Clinical Frailty Scale; DSM-BIA, Direct-Segmental Multi-frequency Bioelectrical Impedance Analyses; GDF, growth differentiation factor; IGF, insulin-like growthfactor; IL, interleukin; OMC, Orientation-Memory-Concentration test; TNF, tumor necrosis factor; SARC-F, sarcopenia screening; SNAQ, Short Nutritional Assessment Questionnaire.

approved by the local ethics committee of Copenhagen and Frederiksberg (H-19039214) and the Danish Data Protection Agency (P-2019-239) and all experimental procedures are performed in accordance with the Declaration of Helsinki. The project complies with the regulations of the General Data Protection Regulation and the Data Protection Act.

All eligible patients receive oral and written information. In the case of severe dementia or delirium, some patients might be unable to provide participant consent.

Table 1 Variables assessed by research personnel and extracted from EPIC or the Danish civil registration system

	Assessed by research personnel	Extracted from EPIC or the Danish Civil Registration System
Descriptive information		
Age		x
Gender		x
Smoking	x	
Emigration		x
Clinical information		
Hospital length of stay		x
Main diagnosis (index admission)		x
Non-elective readmissions within 90 days of discharge		x
Main diagnosis (readmission)		x
In-hospital mortality		x
All-cause mortality within 90 days of index admission		x
Prescribed medications on admission		x
ICD-10 discharge diagnoses 5 years prior to index admission		x
Number of hospitalisations (acute and elective) 1 year prior to the index admission		x
Vital values (saturation, respiratory rate, heart rate, blood pressure, core temperature, Glasgow Coma Scale) on admission		x
Early Warning Score on admission		x
ECG abnormalities on admission		x
Admission to the intensive care unit (admission date, discharge date, treatment with vasopressors, dialysis and mechanical ventilation)		x
Sepsis during the index admission		x
Braden Score		x
Anthropometry and physical function		
Bodyweight (kg)	x	
Height (cm)	x	
Body composition (DSM-BIA)	x	
Whole body phase angle (DSM-BIA)	x	
Handgrip strength (kg)	x	
Sit-to-stand ability	x	
Sit-to-stand ability, categorical	x	
Habitual gait-speed* (m/s)	x	
Canadian Study of Health and Aging Clinical Frailty Scale	x	
SARC-F score	x	
Use of walking aids at index admission		x
Discharge to an increased level of care*		x
Barthel Index at admission*		x
Barthel Index at discharge*		x
Cumulated Ambulation Score*		x
New Mobility Score*		x
De Morton Mobility Index score*		x
Cognition		
Dementia diagnosis		x
Orientation-Memory-Concentration test	x	
Nutrition		
Short Nutritional Assessment Questionnaire	x	
Blood		

Continued

Table 1 Continued

	Assessed by research personnel	Extracted from EPIC or the Danish Civil Registration System
Results of routine blood tests on admission (C reactive protein, albumin, urea, creatinine, haemoglobin, white blood cells, platelets, potassium, sodium, glomerular filtration rate, liver biochemistry, glucose, calcium, magnesium, lactate and other routine blood samples)		x
Results of PROTECT blood tests (TNF-α, IL-6, IL-10, TGF-β, GDF-11, GDF-15, follistatin, IGF-1 and suPAR)	x	

*Variables included in the Geriatric cohort only.
DSM-BIA, Direct-Segmental Multi-frequency Bioelectrical Impedance Analyses; GDF, growth differentiation factor; ICD, International Classification of Diseases; IGF, insulin-like growth factor; IL, interleukin; SARC-F, sarcopenia screening; TGF, transforming growth factor; TNF, tumor necrosis factor.

In these cases, we seek participant consent from a close relative or guardian, should the guardianship include access to sign participant consent for research purposes. Independent medical doctors who have knowledge of the project but are not associated with the project and are independent of the interests of the principal investigator evaluate whether these subjects can participate in the study.

The project entails minimal discomfort and no permanent side effects; thus, it is considered ethically sound. Findings from the project, regardless of the outcome, will be published in relevant peer-reviewed scientific journals ensuring the anonymity of the patients. The study is registered at clinicaltrials.gov where positive, negative or inconclusive results will be published.

DISCUSSION

The importance of sarcopenia has recently been underlined by its inclusion as a reportable disease in the Centers for Disease Control and Prevention (ICD-10-CM code M62.84) in October 2016.[35] Even though the serious consequences of sarcopenia are widely recognised, the diagnose has yet to be implemented in clinical practice in Denmark. Lack of knowledge regarding the basic biological mechanisms driving sarcopenia in conjunction with other age-related diseases and lack of systematic assessment hinders the identification and treatment of sarcopenia and can lead to physical deconditioning during hospitalisation. As such, the knowledge surrounding the prevalence and determinants of sarcopenia in older medical patients is scarce, and it is unknown whether circulating biomarkers, individually or in combination, can predict physical deconditioning during hospitalisation.

Mechanisms that regulate skeletal muscle mass are central to the understanding of sarcopenia. Myostatin, also referred to as GDF-8, is a part of the TGF-β family and predominantly expressed in skeletal muscle. Myostatin and TGF-β are inducers of catabolic processes, inhibiting muscle growth and inducing muscle protein breakdown via activation of the Small Mothers Against Decapentaplegic (SMAD)2 and SMAD3 transcription factors.[36 37] Myostatin is reportedly increased with ageing,[38] and following prolonged bed rest,[39] and treatment with myostatin antibodies attenuates the loss of muscle mass and function induced by immobilisation in mice.[40]

Recently, GDF-11, a TGF-β family ligand,[41] has been measured in human blood samples.[42] High circulating GDF-11 levels have been related to increased disease burden and elevated risk of postoperative complications and mortality in older adults undergoing heart surgery. Notably, patients categorised as physically frail based on low handgrip strength and gait speed as well as self-reported activity measures had significantly higher GDF-11 levels compared with non-frail controls.[42]

GDF-15, another member of the TGF-β family, is present in low levels under healthy conditions but can increase during disease or injury and contribute to muscle wasting by suppressing appetite, which may result in anorexia and drastic weight loss.[43] In older patients, unintentional weight loss has been associated with an increased in-hospital morbidity and increased overall mortality.[44] GDF-15 may be induced in response to cellular stress signals or dysfunctions, and it has been suggested that circulating levels of GDF-15 could be biomarker of mitochondrial dysfunction.[45] Nonetheless, several studies demonstrate that GDF-15 levels are predictors of all-cause mortality.[46 47]

Follistatin acts as an antagonist to TGF-β family ligands including myostatin, TGF-β and GDF-11.[37] Measurements of TGF-β ligands as well as their antagonist follistatin could represent biomarkers of muscle breakdown, physical function or mortality. However, the translation of these findings into clinical utility needs further validation in a larger cohort.

Several studies have investigated the association of inflammatory biomarkers with muscle mass, muscle strength and muscle function in healthy older subjects. Most commonly, studies have focused on a few biomarkers, such as TNF-α, IL-6 or C-reactive protein (CRP).[9 48–50] A recent study has demonstrated an inverse relationship between a composite of proinflammatory and anti-inflammatory markers and muscle mass, strength and function in healthy older subjects.[51] However, results are inconsistent and lack clear evidence as to whether these inflammatory biomarkers are associated with sarcopenia. Nonetheless, circulating levels of CRP are predictive of both the length of hospital stay and readmissions.[52 53] Indeed, geriatric patients with inflammation, evaluated by

CRP levels at admission, stayed on average 3 days longer than patients without inflammation.[54]

The anabolic growth factor, IGF-1, and the IGF-1/phosphatidylinositol 3-kinase(PI3K)/Akt pathway is involved in skeletal muscle hypertrophy and atrophy.[55 56] Circulating IGF-1 levels decrease with ageing, while inflammatory markers such as TNF-α and IL-6 can interfere with the IGF-1 signalling pathway.[57 58] As such, changes in IGF-1/PI3K/Akt signalling during ageing may be a result of decreased IGF-1 expression as well as IGF-1 inhibition. Notably, no difference in circulating IGF-1 concentrations were found between older sarcopenic and non-sarcopenic women.[59]

Recently, suPAR was established as a biomarker of inflammation and immune activation, and elevated levels of suPAR are believed to reflect a state of chronic inflammation.[60] SuPAR correlates with other inflammatory markers, such as TNF-α, and patients with the highest levels of suPAR generally have the worst prognosis.[61] In one study, suPAR was associated with low muscle mass, while IL-6 was associated with low muscle mass and increased fat mass in both patients and healthy controls.[62] Thus, there seem to be distinct inflammatory processes occurring simultaneously with different effects on muscle mass and fat mass, respectively.

Distinct patient populations with coexisting pathophysiological processes might exhibit different biomarker profiles. Further validation needs to be conducted in different patient populations to use the possible prognostic value of these biomarkers, either individually, or in combination with functional and clinical measures. Systematic identification of patients at risk of prolonged hospitalisation and deconditioning should occur to enable early individualised interventions to counteract the adverse outcomes of prolonged bed rest.

Results from the Copenhagen PROTECT study can be helpful in the identification of older patients at risk of prolonged hospitalisation. Additionally, circulating biomarker assays able to predict physical deconditioning during hospitalisation will help in the early detection of geriatric patients at risk of deconditioning during hospitalisation. This knowledge can then be tested in a future interventional study. The Copenhagen PROTECT study is considered feasible, ethically sound, and with potential extensive implications for future identification and treatment of sarcopenia in older medical patients.

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Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

Acknowledgements The authors would like to thank the doctors, nurses, secretaries and physiotherapists at the acute ward and the Department of Geriatric and Palliative Medicine for their cooperation and patience during patient recruitment and assessment. Furthermore, they would like to thank Rasmus Rønnemoes Iversen for his help in the recruitment of patients.

Contributors RSK, CS, MS and FEN drafted the manuscript. CS, FEN, RSK, MS, AE, HN, HA, MRW and EP designed the study. SKH, HA, HN, AE, FH, MRW, EP, TN and CBR contributed to the discussion, edited and reviewed the manuscript. All authors read and approved the final manuscript.

Funding The work is supported by funding from the Novo Nordisk Foundation; grant number NNF18OC0052826.

Disclaimer The funders take no part in the design of the study; in the collection, analysis or interpretation of data; in the writing of manuscripts or decisions regarding publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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