

Sarcopenia in patients with hip fracture

A multicenter prospective study with one-year follow-up

Ole Martin Steihaug

Thesis for the Degree of Philosophiae Doctor (PhD)
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Scientific environment

In 2011 I received a combined position as a researcher at the Kavli Research Center for Geriatrics and Dementia and as a medical doctor specializing in geriatrics at Haraldsplass Deaconess Hospital. The Kavli center received funding from the city of Bergen, Haraldsplass Deaconess Hospital and the Kavli foundation. In 2014, I became a PhD student at the medical faculty at the University of Bergen with funding from the Western Norway regional health authority. I am grateful for the opportunity to be part of the research center and to be a PhD student. Bergen Research Group in Geriatrics/Bergen's Oldest (BOLD) was founded in 2015 with the aim of coordinating and facilitating geriatric research at the University of Bergen. Being part of a group of like-minded fellow physicians doing research in geriatrics has been key to my development as a researcher.



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Bård Bogen has laid a lot of the groundwork for the study including writing the first draft of the research protocol. He has taught me about physical performance and the methodology of physical performance testing.

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Bergen, March 18, 2018

Ole Martin Steihaug

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Abbreviations

ALM	Appendicular lean mass
ASA score	American Society of Anesthesiologists physical status classification system
AUC	Area under the curve
B-ADL	Barthel activities of daily living
BIA	Bioelectrical impedance analysis
BMI	Body mass index, kg/m ²
CT	Computerized axial tomography
DXA	Dual-energy X-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older Persons
FNIH	Foundation of the National Institute of Health
LOA	Limit of agreement
MRI	Magnetic resonance imaging
NMS	New Mobility Score
NRS 2002	Nutritional risk score 2002

List of publications

- I. Steihaug OM, Gjesdal CG, Bogen B, Ranhoff AH. Identifying Low Muscle Mass in Patients with Hip Fracture: Validation of Bioelectrical Impedance Analysis and Anthropometry Compared to Dual Energy X-ray Absorptiometry. *J Nutr Health Aging*. 2016;20(7):685-690.
- II. Steihaug OM, Bogen BE, Kristoffersen MH, Ranhoff AH. Bones, Blood and Steel: How Bioelectrical Impedance Analysis is affected by Hip Fracture and Surgical Implants. *J Electr Bioimp*. 2017;8(1):54-59.
- III. Steihaug OM, Gjesdal CG, Bogen B, Kristoffersen MH, Lien G, Ranhoff AH. Sarcopenia in patients with hip fracture: A multicenter cross-sectional study. *PLoS One*. 2017;12(9):e0184780.
- IV. Steihaug OM, Gjesdal CG, Bogen B, Kristoffersen MH, Lien G, Hufthammer KO, Ranhoff AH. Does sarcopenia predict change in mobility after hip fracture? a multicenter observational study with one-year follow-up. *BMC Geriatrics*. 2018;18(1):65.

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Abstract

Sarcopenia is a geriatric syndrome of reduced muscle mass and physical performance associated with falls, fractures, impairments in activities of daily living, and mortality. Hip fractures are fractures of the upper third of the femur and typically occur in older persons after a fall. They are associated with lifelong impairments of mobility, mortality and risk of institutionalization. Hip fractures are common, preventable and in many places receive suboptimal care. This thesis is based on the research project sarcopenia in patients with hip fracture. The project is a prospective study with one-year follow-up on older acute hip fracture patients living in the community, admitted at three hospitals: Haraldsplass Deaconess Hospital and Haukeland University Hospital in Bergen and Diakonhjemmet Hospital in Oslo, Norway in the period of 2011-2013. The aim of this thesis is to investigate sarcopenia as a clinically useful risk factor for adverse clinical outcomes after hip fracture.

Our findings are presented in four papers. In the first paper we studied anthropometry and bioelectrical impedance analysis for determining muscle mass in patients with hip fracture, using dual-energy X-ray absorptiometry as the reference method. We found that muscle mass measured by single frequency bioelectrical impedance and anthropometry can identify patients with low muscle mass, which is a necessary step in assessing sarcopenia at the bedside.

In the second paper we investigated how hip fracture, surgical repair and surgical implants affected measurements by bioelectrical impedance analysis. Bioelectrical impedance analysis on the same side of the body as the fracture was affected in the days after surgery, but not after three months. Measurements by bioelectrical impedance analysis were not affected by type of surgical implant. Our findings support the use of bioelectrical impedance analysis in subjects who live with surgical implants and after surgery. We recommend measuring the unfractured side if bioelectrical

impedance analysis is used to determine body composition in the days after hip fracture surgery.

In the third paper, we assessed the feasibility of determining sarcopenia in postoperative patients with hip fracture, and the prevalence of sarcopenia. Sarcopenia status, estimated by anthropometry, grip strength and self-reported pre-fracture mobility, was assessed in 202 out of 282 participants. The prevalence of sarcopenia was 37% and associated with increasing age, comorbidities and malnutrition. There was no difference in the prevalence of sarcopenia by sex, but men with hip fracture had a higher prevalence of low muscle mass. Our findings support sarcopenia as a clinically relevant risk factor after hip fracture.

In the fourth paper, we investigated how sarcopenia status predicted change in mobility and other clinical outcomes at one year after hip fracture. Sarcopenia did not predict change in mobility. Participants with sarcopenia had lower mobility and more impairments in activities of daily living and an increased risk of becoming a resident of a nursing home and death. Pre-fracture mobility predicted mobility at one year. Sarcopenia needs further validation in patients with hip fracture by exploring other definitions, techniques and cut-points in order to estimate future risk and provide personalized medicine. We recommend that all hip fracture patients have their pre-fracture mobility assessed to determine their risk of adverse outcomes and as a benchmark for successful rehabilitation.

This thesis expands the knowledge about sarcopenia to a vulnerable group of patients. Our findings support sarcopenia as a clinically relevant risk factor in acute hip fracture patients. Determining sarcopenia is feasible, it is prevalent in patients with hip fracture and it is associated with comorbidities, malnutrition, mobility and becoming a resident of a nursing home.

Sammendrag på norsk

Sarkopeni er en aldersrelatert tilstand hvor personer har lite muskelmasse, redusert muskelstyrke og redusert fysisk yteevne, noe som er assosiert med fall, brudd, redusert evne til å klare seg selv i dagliglivet og økt fare for død. Hoftebrudd er brudd i øverste del av lårbenet og skjer typisk hos eldre etter et fall fra egen høyde. Hoftebrudd er assosiert med varig nedsatt gangfunksjon, økt dødelighet og økt fare for å komme på sykehjem. Hoftebrudd er vanlig, kan forhindres, og mange pasienter med hoftebrudd får ikke optimal behandling. Denne doktorgradsavhandlingen er basert på forskningsprosjektet sarkopeni hos pasienter med hoftebrudd. I denne studien har vi undersøkt sammenhengen mellom sarkopeni, hoftebrudd og gangfunksjon hos 282 pasienter innlagt med hoftebrudd ved Haraldsplass Diakonale sykehus, Haukeland universitetssjukehus og Diakonhjemmet sykehus i årene 2011-2013, med ett års oppfølging. Vår hypotese er at sarkopeni er en relevant risikofaktor for dårlig prognose etter hoftebrudd.

Avhandlingen består av fire artikler. I den første artikkelen ønsket vi å finne enkle måter å fastslå muskelmasse etter hoftebruddet. Vi sammenlignet bioelektrisk impedans og antropometri med røntgengjennomlysning. Vi fant at antropometri og bioelektrisk impedans var i stand til å identifisere deltagerne som hadde lav muskelmasse, noe som er nødvendig for å kunne fastslå sarkopeni hos sengeliggende pasienter.

I den andre artikkelen analyserte vi hvordan hoftebrudd og kirurgi påvirket målinger med bioelektrisk impedans. Målinger ved bruk av bioelektrisk impedans utført på samme kroppshalvdel som hoftebruddet ble påvirket i dagene etter hoftebruddet, men ikke etter tre måneder. Målingene ble ikke påvirket av typen kirurgisk implantat som ble benyttet. En praktisk løsning på dette er å måle den motsatte kroppshalvdelen til hoftebruddet. Bioelektrisk impedans kan brukes hos pasienter med kirurgiske implantater og hos pasienter som nylig har gjennomgått hoftebrudd.

I den tredje artikkelen undersøkte om det er mulig å fastslå sarkopeni hos postoperative pasienter med hoftebrudd og prevalensen av sarkopeni hos disse. Vi undersøkte for sarkopeni ved å bruke antropometri, gripestyrke og selvrappert gangfunksjon hos 202 av 282 deltagere og fant at 37 % hadde sarkopeni. Sarkopeni var mer vanlig ved økende alder, hos dem med flere kroniske sykdommer eller med tegn til underernæring. Det var ingen forskjell i forekomsten av sarkopeni mellom kvinner og menn, men menn med hoftebrudd hadde økt risiko for å ha lav muskelmasse. Disse funnene understøtter at sarkopeni er en relevant risikofaktor hos pasienter med hoftebrudd.

I den fjerde artikkelen undersøkte vi om sarkopeni fører til at gangfunksjonen forverres ett år etter hoftebruddet. Sarkopeni fører ikke til ytterligere forverring av gangfunksjonen, men gangfunksjonen var dårligere hos dem med sarkopeni sammenlignet med dem uten. Sarkopeni var forbundet med redusert evne til klare dagliglivets aktiviteter og økt risiko for å komme på sykehjem eller død. Vi anbefaler at det forskes mere på sarkopeni hos pasienter med hoftebrudd ved å utvikle andre måter å måle sarkopeni på, til bruk i risikovurdering og til persontilpasset behandling. Vi anbefaler at gangfunksjonen før bruddet brukes til å forutsi fremtidig gangfunksjon og brukes som et mål på vellykket rehabilitering.

Denne doktorgradsavhandlingen har bidratt til å belyse forekomsten av sarkopeni hos pasienter med hoftebrudd. Den har vist at sarkopeni er mulig å måle, er assosiert med komorbiditet, underernæring, redusert gangfunksjon og økt risiko for å flytte på sykehjem. Våre funn styrker hypotesen om at sarkopeni er en relevant risikofaktor for dårligere prognose etter hoftebrudd.

1. Introduction

Good health is associated with having a reserve capacity that enables us to tolerate injury. As we grow older our bodies undergo a dynamic process of damage and repair. With increasing age, we accumulate injuries which lead to increased vulnerability, loss of function, disablement, illness and eventually to death (1, 2). The resources and mechanisms that prevent or slow this process of disablement are multifactorial and dependent on factors intrinsic, and extrinsic to the individual. Examples of bodily reserves are excess lung capacity reducing the frequency of respiratory failure in pneumonia and good cognitive function reducing the risk of delirium after surgery. Motivation, health literacy, leisure time, money, and a physical environment that enable an intellectual, physical, social and emotional fulfilling life are also factors that protect against developing disability. If injury and illness occur, these same factors facilitate healing and rehabilitation, and minimize the risk of the injury or illness recurring (3). Several conceptual models have been developed for the process of health, illness and disability, among them the one by Verbrugge and Jette reproduced in figure 1 (2), and the World Health Organization International Classification of Functioning, Disability and Health (3).

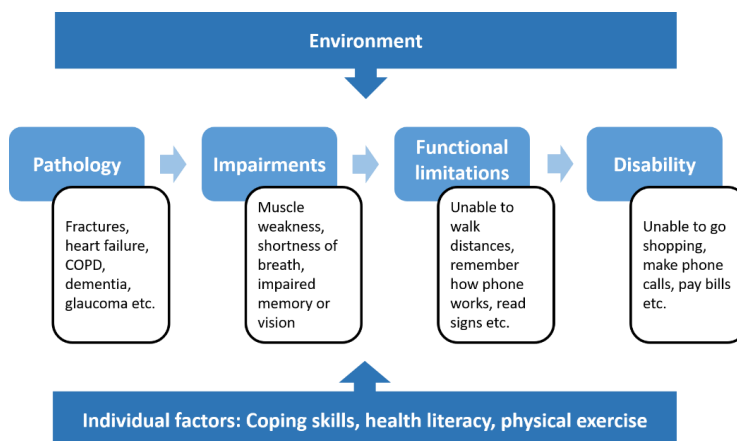


Figure 1: The disablement process. After Verbrugge and Jette (2).

Loss of mobility is a common, age-related condition that is closely associated with disability (4). One quarter of the Norwegian population aged ≥ 67 report that they are unable to walk for 5 minutes or ascend a flight of stairs without pausing (5). This thesis is about how two age-related phenomena, sarcopenia and hip fractures, contribute to poor health. Sarcopenia is the loss of muscle mass and physical function, and is associated with falls, fractures (6) and loss of mobility (7). Hip fractures are common fall-related injuries leading to a loss of mobility (8). In the disablement process described by Verbrugge and Jette (2), sarcopenia and hip fracture are pathological processes which lead to reduced mobility, functional limitations and disability. This thesis examines sarcopenia in acute hip fracture patients, included at three Norwegian hospitals and followed for one year.

1.1 Hip fracture

Mrs. Olsen, 82 years old, trips and falls during a bathroom visit. She is not able to react quickly enough to regain her balance and she lands on the lateral aspect of her left hip. Unable to get up from the floor, she calls for an ambulance and is taken to hospital. She is given morphine and has an X-ray of her hip. The X-ray shows an undisplaced fracture of the neck of femur. Mrs. Olsen is operated on in spinal anesthesia the next morning and receives two pins to stabilize the fracture in the anatomical position. After 6 days in hospital she is discharged to the rehabilitation ward of a skilled nursing home. She spends another four weeks there before returning home. At home, she receives weekly care visits for help in showering and managing her medication. Her walking ability slowly improves over the next year, but she rarely moves out of the house and is dependent on her rollator.

1.1.1 Etiology of hip fractures

A hip fracture is a fracture of the upper part of the femur (including the neck of femur, trochanter and sub-trochanteric region). See figure 2. They usually result from a

sideways fall from standing height or lower with the impact on the greater trochanter (9, 10).

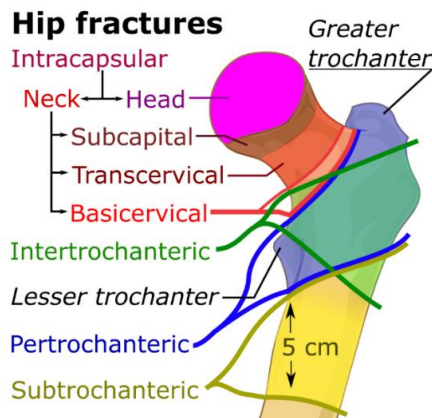


Figure 2: Proximal femur indicating types of hip fractures. Image by Mikael Häggström. In the public domain.

A person who has lost their balance and is about to fall will usually be able to undertake protective maneuvers such as landing on the outstretched arm or turning their upper body in the direction of the fall to prevent fractures and other traumatic injuries (9, 11). Many falls are caused by extrinsic factors, such as trips or stumbles (12) and in 15% of falls the cause would also have led a fit person to fall (13). Some falls have a single precipitating cause such as symptomatic orthostatic hypotension, acute stroke with paralysis, or other acute illness (14), but most falls are the result of several interacting causes (15). Falls are common in the older population with 1/3 of the population aged >65 years experiencing a fall each year, and 50% of the population aged >80 years falling each year. About 10% of persons who fall suffer serious injuries and 2% suffer a hip fracture (16).

Risk factors for falls and fractures

Risk factors for hip fracture can be organized into risk factors for falls and risk factors related to bone quality (17). See table 1. There are several risk predictions scores for

fractures such as the FRAX score, QFracture and the Garvan (18). These include risk factors such as female sex, age, body mass index (BMI), prior fragility fracture, previous falls, current tobacco smoking, use of oral glucocorticoids, comorbidities, secondary causes of osteoporosis, alcohol consumption and bone mineral density.

The risk factors for falls include previous falls, reduced mobility, vertigo, Parkinson's disease or use of antiepileptic drugs (19). The European Union Geriatric Medicine Society recommends screening older adults for risk of falls and bone fragility and one study found that using sarcopenia assessment with FRAX can improve the prediction of fracture risk (20). Current guidelines do not recommend determining sarcopenia to estimate the risk of hip fracture (21).

Table 1. Risk factors for falls and fractures

	Risk factors for falls	Risk factors for fractures
Female gender	X	X
Maternal hip fracture		X
Increasing age	X	X
Low BMI	X	X
Weight loss		X
Low bone mineral density		X
Low gait speed	X	
Previous falls	X	
Previous fracture		X
Reduced muscle strength	X	X
Inappropriate medications	X	
Functional impairment	X	
Use of walking aid	X	
Cognitive impairment	X	
Poor balance	X	
Depression	X	
Poor self-rated health		X

Table 1. Adapted from papers by Tinetti and Kumar and Cummings et al (22, 23).

1.1.2 Epidemiology of hip fractures

Hip fractures are an important cause of poor health and early death in older persons (24, 25). There are approximately 9,000 hip fractures a year in Norway (26). The incidence in Norway is among the highest in the world (27) with an age-adjusted rate of 74 per 10,000 person-years in women and 35 per 10,000 person-years in men (28) and a lifetime risk of hip fracture of 18% in men and 30% in women (29). Most occur in women older than 80 years (28). Approximately 25% of all patients are residents of a nursing home before the fracture (30). The causes of the high incidence of hip

fractures in Norway compared to other countries are undetermined (28). The cost of health care and social services for a patient living in the community before the fracture is estimated at 500,000 NOK in the first year increasing to 1,000,000 NOK after two years (31).

1.1.3 Consequences of hip fracture

A hip fracture has been described as “a life breaking event” by patients, with feelings of vulnerability, dependency and disruption of normal life (32). Prognosis after hip fracture is related to the vulnerability of the patient, the fracture itself, and the treatment she receives. This includes surgery, rehabilitation and interventions to reduce the risk of adverse outcomes. A hip fracture is painful and the average pain score in the emergency department is 7 on a scale from 0 to 10 (33). Around 30% of the patients have pain and trouble sleeping due to pain 6 months after the fracture (34). Good pre-fracture mobility and self-reported health are strong determinants of successful recovery of mobility, whereas poor mobility increases the risk of becoming dependent in activities of daily living and becoming a resident of a nursing home (35). It takes 6-12 months before maximal recovery of mobility is achieved, but half of all patients do not regain their pre-fracture level of mobility (8, 36). Geriatric ward care (37) and extended progressive strength training improves mobility (38). Fear of falling is a condition where concern about falling leads one to avoiding activities that could lead to a fall (39). After hip fracture around half of patients suffer from a fear of falling (40). Fear of falling is associated with falls, impairments in activities of daily living, not being able to walk outdoors, becoming a resident of a nursing home. and mortality (41). Physical exercise and geriatric care reduces the fear of falling (42, 43). A hip fracture leads to a reduced quality of life and impairments in activities of daily living (8, 44). Around half of the patients will need assistance in their own home and 20-30% will lose the ability to make their own meals (8). Among those who live in their own home before the fracture, 15% become residents of a nursing home after the fracture and up to half will have moved to some sort of supported living arrangement (8). Some 10% of the patients are readmitted to hospital within 30 days of discharge (45).

Approximately 10% of patients undergo revision hip surgery (46). A fracture is a risk factor for subsequent fractures (47). In Norway, it is estimated that the 10 year risk of a second hip fracture is 15% for women and 11% for men (48). Mortality in the year after hip fracture is 10-30% (25) which is greater than for myocardial infarction and similar to that of stroke (49). Risk factors for mortality are male gender, increasing age, higher American society of Anesthesiologists (ASA) score, greater number of comorbidities, malnutrition, and limitations in activities of daily living (50). Common causes of death in hospital after hip fracture are pneumonia, heart failure, myocardial infarction and pulmonary embolism (51). In younger patients the relative risk ratio for mortality is increased, but the absolute increase in risk is greater in older patients (52). It is estimated that the excess mortality of patients with hip fracture constitute 5% of the mortality in the Norwegian population aged 50 years and older (25). Hip fractures account for a loss of 2.7% of the healthy life expectancy in older persons, which is of the same magnitude as breast cancer (24).

1.1.4 Treatment of hip fractures

Reducing the burden of hip fracture requires reducing the risk of having a hip fracture, optimal acute treatment, good rehabilitation and preventing complications (53).

Surgery is the primary treatment of hip fracture (54). When the proximal femur is fractured the tension of the surrounding muscles pull the parts of the femur apart.

Surgical treatment involves restoring normal anatomy by fixing the fracture in place with surgical implants to restore mobility and reduce pain. Surgical implants are mainly composed of metal and sometimes have plastic, hydroxyapatite or ceramic components. See figure 3 and 4 for commonly used surgical implants in treatment of hip fractures.



Figure 3: Surgical implants used for hip fracture repair. From left: hemiarthroplasty of the hip, two cannulated screws and a compression hip screw. Photo: Ole Martin Steihaug.

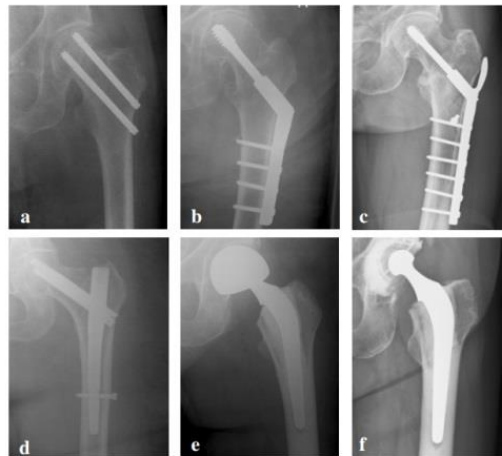


Figure 3. Operation methods for hip fractures. Radiograms of different type of implants:

- a. Osteosynthesis with 2 screws
- b. Osteosynthesis with hip compression screw
- c. Osteosynthesis with hip compression screw with lateral support plate
- d. Osteosynthesis with intramedullary nail
- e. Hemiarthroplasty
- f. Total hip arthroplasty

Fig. 4: Plain film X-rays of hip fractures treated with surgical implants. From JED. Gjertsen (55). Reproduced with permission.

Treatment has undergone substantial changes in the last decades with a reduction in rates of reoperations and mortality in the period 2005-2014 reported in a study from the Norwegian Hip Fracture Register (56). The quality of treatment in Norway is comparable to other developed countries. The 30-day mortality rate after admission for acute hip fracture is at 8% (57) compared to 7% in England and Wales (58).

Orthogeriatric care of hip fractures

Orthogeriatric care is the current best practice care for patients with hip fracture (53). Orthogeriatrics is shorthand for the multidisciplinary collaboration between orthopedic surgeons, geriatricians and other healthcare worker in the care of older patients with fractures. Comprehensive geriatric assessment is a cornerstone of geriatric treatment. It is the process of identifying the patient's preferences and challenges and to improve outcomes by managing complications, rehabilitation, comorbidities, medications and preventing falls (59). Studies have shown less delirium (43), better physical performance (43), economic benefits (43) and reduced mortality (60) for patients receiving orthogeriatric care compared to traditional orthopedic care. Orthogeriatric care is slowly becoming more common in Norway after two important intervention trials (43, 61). The Oslo Orthogeriatric Trial (61) was a randomized intervention study of orthogeriatric care compared to orthopedic care. The hypothesis was that orthogeriatric care would lead to improved cognition after 4 months. There was no effect of orthogeriatric care on cognition, but a beneficial effect on physical performance for participants living in the community. The Trondheim hip fracture trial found that the participants who received orthogeriatric care had better physical performance at four months (43). This difference was maintained at 12 months and was more pronounced among younger, female patients with less impairments in activities of daily living before the fracture (62).

Rehabilitation and aftercare

With the increasing age of the population, older persons are living longer with reduced mobility and other complications of hip fracture (52). Progressive strength training and other forms of exercise rehabilitation for several months after hip fracture improves physical performance (63). One small study found that close follow-up by a geriatrician and physical exercise in the year after hip fracture improved physical performance, independence in activities of daily living, and reduced the risk of nursing home admission and mortality (64). Reducing the risk of falls by exercise programs leads to a reduced risk of fracture (65) and is supported by the European Union Geriatric Medicine Society (21). Supplemental vitamin D and calcium provides a small reduction in the risk of fractures (66). Hip protectors, padded underwear, reduce the risk of hip fracture for persons living in institutions (67). Fractures can be prevented by targeted screening and treatment of osteoporosis (68). This is also true for second hip fractures (69). Use of anti-osteoporosis drugs reduces the risk of hip fracture by 30-50% (70, 71). Among Norwegian hip fracture survivors living in the community 4% of men and 15% of women received a prescription for an anti-osteoporosis drug in 2005 (72). This compares unfavorably with the UK, where 97% of patients are considered for drug treatment (58).

1.2 Sarcopenia

Mrs. Olsen is evaluated in the orthopedic ward 4 days after surgery for hip fracture. She can rise from a chair with assistance and walk slowly along the hallway using a rollator and a member of staff by her side to support in case she loses her balance. Her handgrip strength is 14kg and her appendicular lean mass by anthropometry is 5kg/m². She has sarcopenia. What are the implications of her sarcopenia diagnosis? How does sarcopenia status differ from nutritional risk and frailty?

Sarcopenia is associated with falls and falls are associated with hip fracture. Sarcopenia is an age-related decline in muscle mass and physical function (73). Skeletal muscle can be considered an organ constituting 40% of the body weight and requiring 30% of basal energy expenditure. Skeletal muscle enables locomotion, manipulation of the environment, breathing, communication, thermoregulation and is a nutrient store (74). Sarcopenia is a risk factor for reduced mobility and death (7). Sarcopenia has received increasing attention since it was described by Irwin Rosenberg in 1988 (75). It was originally described as a syndrome of reduced muscle mass (75), but definitions have developed to also included reduced strength and reduced physical performance (76). Janssen et al defined sarcopenia as low muscle mass relative to body mass (73), the European Working Group on Sarcopenia in Older Persons (EWGSOP) defined sarcopenia as low muscle mass and either low muscle strength or physical function (77). The Foundation of the National Institute of Health (FNIH) sarcopenia project defined sarcopenia as low muscle mass with low muscle strength (78). Sarcopenia has recently been recognized as a health related condition with its own International Classification of Diseases code, M62.84 (79). The EWGSOP definition describes primary and secondary sarcopenia. Primary sarcopenia has no evident cause, except for aging. Secondary sarcopenia is a result of identifiable processes such a malnutrition, bed-rest or chronic diseases.

1.2.1 Pathophysiology of sarcopenia

The pathophysiology of sarcopenia is complex and only partially determined (80). Physical performance is made possible by the interaction of several organs and systems. Physical performance and sarcopenia is influenced by hereditary (81) as well as environmental factors (82). Sarcopenia status is influenced by socioeconomic status and depressive symptoms (83, 84) as well as specific behaviours such as excessive alcohol intake (85) or smoking (86). An important feature is the relative loss of type 2 muscle fibres, which are known as “fast twitch” fibres that are important for explosive

muscle contraction necessary to prevent falls (87). Chronic low grade inflammation is associated with sarcopenia, possibly by disturbing the balance of protein synthesis and catabolism (88), leading to anorexia, proteolysis and lipolysis. The endocrine system causes sarcopenia by influencing muscle metabolism and inflammation (89).

Deficiencies in the sex hormones estrogen and testosterone, growth hormone, thyroid hormone, PTH and vitamin D are associated with sarcopenia (89, 90). The prevalence of obesity, diabetes mellitus type 2 and sarcopenia all increase with increasing age (91). Muscle is one of the most important regulators of blood glucose (92), and loss of muscle mass leads obesity and diabetes mellitus type 2 that are associated with a further loss of muscle mass (93). Several brain functions are necessary for performing physical activity such as motivation and alertness, initiation of movement, sensation and perception, and coordination of movement (94). Examples of diseases contributing to sarcopenia by acting on the brain are Alzheimer dementia, Parkinson disease and stroke. The brain is dependent on the peripheral nervous system for transmitting the signals from the brain to the muscles by the neuromuscular junction, which undergoes a process of degeneration leading to loss of motor units and motor fibres (95). The muscles and nervous system are dependent on blood flow by the cardiovascular system, which can be affected by heart failure or atherosclerotic disease (96). At the level of the muscle, sarcopenia is associated with a reduced pool of satellite cells leading to lower regenerative potential after injury (97) and reduced capillarization of skeletal muscle, leading to impaired transport of nutrients and waste products (98).

1.2.2 How to diagnose sarcopenia

Sarcopenia is not currently a routine part of diagnosis, prognostication or treatment, but several expert groups recommend that it should be (73, 77, 99, 100). The recommended approach is to first determine physical performance, then muscle strength and lastly muscle mass, only moving on to the next step if the result of the previous step is abnormal. In this thesis we have adhered to the recommendations of the EWGSOP that to have sarcopenia one must have low muscle mass and one of either low muscle strength or physical function (73).

Measuring muscle mass

Low muscle mass is mandatory for diagnosing sarcopenia (73). It can also be the aspect of sarcopenia which is most difficult to measure. In this thesis we have assessed appendicular lean mass (ALM), which typically constitutes 75% of total body muscle mass (101). Typical values for ALM are 23kg for older men and 16kg for older women (77). Muscle mass varies with body size, and this has led to different approaches to define low muscle mass relative to body size such as ALM/weight, ALM/height² and ALM/BMI, or muscle mass relative to fat mass (102). There is disagreement about what technologies are precise enough to measure muscle mass, while still being feasible in clinical use. Dual-energy X-ray absorptiometry (DXA) measures lean mass as a function of how the body stops X-ray beams of two different energy levels. This creates a two-dimensional image where bone is white, fat is dark and lean mass is grey. DXA is used to determine total body muscle mass by assessing the non-bone, non-fat compartment of the arms and legs known as ALM (103). The radiation exposure of a whole body DXA scan is comparable to one day of background radiation at sea level (104). ALM by DXA has good precision with a coefficient of variation of 3% (105), and muscle mass by DXA will usually be within 2kg of that measured by magnetic resonance imaging (MRI) (106, 107). DXA has been used to detect small changes in muscle mass in repeated measures (108). Muscle mass by DXA is sensitive to changes in muscle water content, such as seen with dehydration (109) or carbohydrate loading (109). The European Society for the Clinical and Economic Aspects of Osteoporosis and Osteoarthritis working group on frailty and sarcopenia have recently stated that DXA is the reference standard for measuring muscle mass (101).

Anthropometry is an established and commonly used method for determining body composition (110). The most widely used anthropometric method is to determine BMI, as body weight divided by height squared. Measuring weight and height can be challenging in patients who are immobile in bed. Using BMI, one can estimate the

presence of a large fat mass compartment in cases with high BMI, and low muscle mass and low-fat mass with a low BMI. More advanced anthropometric techniques involve measuring the circumference of different body parts, such as the upper arm, calves, or the abdomen, and skinfold thicknesses with calipers. In obese subjects with large amounts of superficial adipose tissue it is challenging to estimate skinfolds accurately (111). Test-retest correlation coefficient of variability is typically 10% for triceps skinfold and 1% for midarm circumference (112). Anthropometry for determining muscle mass has been validated using MRI (113), DXA, urinary creatinine excretion (112) and underwater weighing (114). Muscle mass estimated by anthropometry is usually within 6kg of muscle mass measured by MRI (113).

Bioelectrical impedance analysis (BIA) is a technique for measuring body composition based on how a weak alternating current is affected by moving through the body (115). Body fat has high resistance, whereas muscle is a conductor. BIA is an established technology for determining muscle mass and is in common use by laypersons and geriatricians (110, 116). It is safe, non-invasive, quick and inexpensive. BIA is highly reproducible with a reported coefficient of variation of 1-2% within one day for resistance (115). Several epidemiological studies have used BIA to determine muscle mass (117), and it is able to determine muscle mass at a group level (118). BIA has poor precision in determining serial changes in muscle mass as seen in studies on persons undergoing exercise interventions, weight loss or hemodialysis (119-121). A systematic review cautioned against using BIA to detect changes in muscle and estimated that BIA could detect a change in the mass of a body compartment of 2kg (122). The typical changes in ALM seen in intervention studies are smaller than this and are frequently less than 1kg (123). Expert opinion recommends that BIA is used as a screening tool to identify persons with low muscle mass (124). Different BIA devices have different number and placement of electrodes on the body, use different frequencies, voltages and currents, and have the patient standing or lying. Many BIA devices use proprietary algorithms for converting their electrical measurements into estimates of body composition. For this thesis we have used single frequency BIA

devices with four electrodes, converting the raw electrical measurements of resistance and reactance into ALM.

Other methods for determining muscle mass are computerized axial tomography (CT), ultrasound and creatinine excretion. CT enables quantification of individual muscle size, density and amount of fat infiltration (114). CT involves a greater radiation exposure compared to DXA. Ultrasound can accurately measure the cross-section of superficial skeletal muscles such as the rectus femoris muscle (125). It can be used at the bedside and the sensitivity to change is good (126). Historically, the excretion of creatinine in urine measured over several days has been used to estimate muscle mass (114).

Measuring muscle strength

Handgrip strength is a surrogate measure of whole body muscle strength and has been shown to have good test characteristics (127). The clinically important difference in grip strength has been proposed to be 6kg (127). The Southampton protocol describes how one should measure grip strength (127), but it is not uniformly used (110).

Handgrip strength is the only recommended method for measuring muscle strength by the EWGSOP and the FNIH sarcopenia project (73, 77). The FNIH sarcopenia project recommends cut-points for low grip strength of <16kg for women and <26kg for men, whereas the EWGSOP recommends <20kg for women and <30kg for men. There is some confusion in the literature whether the EWGSOP cut points should be operationalized as <20kg and <30kg, or ≤ 20 kg and ≤ 30 kg, but the practical difference is minimal. The cut-points of ≤ 20 kg and ≤ 30 kg have been used in 16 out of 17 studies on European populations (110) and are the cut-points used in this thesis. There is interest in using lower extremity strength instead of handgrip strength, but this is not current practice (128).

Measuring physical performance

Physical performance, such as gait speed, is strongly predictive of future adverse events (129). Studenski et al described a continuous graded influence of habitual walking speed on mortality risk (130) and that improvement in walking speed led to reduced mortality (131). The EWGSOP recommends several different objectively measured methods for determining physical performance such as the Short Physical Performance Battery, usual gait speed, Timed get-up-and-go test and the Stair climb power test (73). The EWGSOP does not consider how to determine physical performance in cases where objective tests are challenging, such as in acute hip fracture.

1.2.3 Epidemiology and natural progression of sarcopenia

Maximal muscle mass is achieved at age 20-40 years and remains stable until age 70 years, when it starts to slowly decline. Muscle strength has a more rapid decline with age compared to muscle mass (132). Older men have more muscle mass and are stronger than women of the same age (133). There are differences in muscle mass by geographical region with muscle mass being lower in individuals from Asian populations, compared to European populations (134). The prevalence of sarcopenia has been studied in older persons living in the community, in institutions and in hospitals (135). Mijnders et al, reporting on a population-based study from Iceland, found an increase in the prevalence of sarcopenia from 7% to 17% from age 75 to 80 years and that engaging in moderate and vigorous physical activity prevented the development of sarcopenia (136). A systematic review on the prevalence of sarcopenia by EWGSOP criteria found a prevalence of 1-29% in persons living in the community, 14-33% in those living in long-term care institutions and 10% for those in acute hospital care (78). Jacobsen et al found a prevalence of sarcopenia of 30% in a Norwegian population of hospitalized older persons (137). In most of these studies the prevalence of sarcopenia increased with age, but the effect of sex varied.

1.2.4 Related syndromes

Frailty

Frailty is a syndrome characterized by increased vulnerability to stressors like illness and trauma and is used for evaluating the health of an older person beyond what is possible by age, disease severity or comorbidities. Frailty is more common in women and the prevalence increases with age (138). There are several definitions of frailty, but the two dominant ones are the Fried criteria, also known as the phenotype model (139), and the cumulative deficit model (140). The cumulative deficit model has been described as the “the more things individuals have wrong with them, the more likely they are to be frail” (141). The 5 Fried criteria describe a physical phenotype which includes weight loss, low grip strength, self-reported exhaustion, slow walking speed and low physical activity. If no criteria are present a person is described as robust, and if a person fulfils 3 or more criteria they are frail. Sarcopenia is considered the aspect of frailty related to physical performance and muscle mass (142). Benefits to classifying older adults by frailty status is to improve risk estimation, to target preventive actions, or as a model of public health (59, 143). Assessing frailty is becoming a routine part of treatment of older persons and is recommended by several disease specific guidelines, such as for colon cancer (144) heart failure (145) and aortic stenosis (146).

Cachexia

Cachexia is characterized by a rapid and substantial loss of lean muscle mass and is caused by specific diseases such as advanced cancer or late-stage organ failure. Sarcopenia and cachexia are distinct conditions, but frequently concurrent. In contrast to cachexia, sarcopenia is age-related, multifactorial and slowly progressive. Other features of cachexia are reduced strength, anorexia, fatigue and elevated inflammatory markers such as C-reactive protein or interleukin-6 (147).

Malnutrition

Malnutrition and sarcopenia frequently coexist and share many characteristics such as increased mortality, low albumin and low BMI (137, 148-150). Hemoglobin and serum albumin are biomarkers of malnutrition and are closely associated with muscle mass and physical performance (149). Figure 5 shows how sarcopenia can be related to malnutrition. The latest statement of the European Society for Clinical Nutrition and Metabolism on malnutrition recommends using low muscle mass, defined as fat free mass index of $<15\text{kg/m}^2$ in women and $<17\text{kg/m}^2$ in men, as one method for diagnosing malnutrition (151). Optimizing nutritional status has promise as treatment of sarcopenia (152).

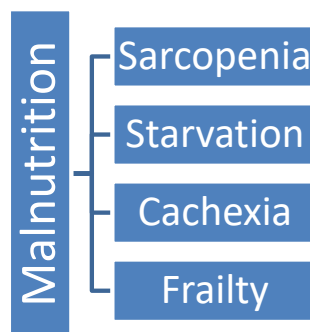


Figure 5: Sarcopenia as one category of malnutrition. Adapted from ESPEN guidelines (151).

Sarcopenic obesity

Sarcopenic obesity describes a phenotype where the person has a large body fat percentage, and a relatively low muscle mass component with low muscle strength and physical performance (153). Obese older persons develop greater impairments of activities of daily living compared to normal-weight persons (152, 153), and have greater risk of falls (154) and hip fracture (155). The FNIH sarcopenia project addresses sarcopenic obesity by recommending cut points for low muscle mass as ALM divided by BMI. Most persons with low muscle mass have a low BMI while

many with sarcopenic obesity have a high BMI. Sarcopenic obesity complicates the assessment of sarcopenia status. Measuring muscle mass by anthropometry is less precise in persons with large amounts of subcutaneous adipose tissue (111). Some research suggest that intramuscular fat is stronger predictor of strength than muscle size (154). Intramuscular adipose tissue can only be assessed by CT or MRI. Muscle strength increases with increasing BMI, and the EWGSOP has recommendations for cut-points for low grip strength by category of BMI (73).

1.2.5 Sarcopenia in clinical practice

In predicting adverse outcomes

Muscle mass, muscle strength and physical performance are interrelated and have different relationships to adverse outcomes. Muscle mass has a weak association with disability and mobility, but is associated with muscle strength (77), which in turn is a stronger predictor of adverse outcomes than muscle mass (77). Physical function, such as gait speed, predicts disability and death (129, 130). Sarcopenia is associated with developing reduced mobility, impairments in activities of daily living, increased rates of hospitalizations, fractures, becoming a resident of a nursing home and mortality (155). Sarcopenia is associated with falls (156, 157) and a possible explanation is a reduced ability to initiate explosive muscle contractions to regain balance (21). A systematic review and meta-analysis of prospective studies on sarcopenia by the EWGSOP criteria found an odds ratio of 3.6 for mortality in 11 studies and an odds ratio of 3.0 for functional decline in 6 studies (135).

Prevention and treatment of sarcopenia

The principal method of preventing sarcopenia is physical activity and exercise (158, 159). Few interventional trials have used sarcopenia status as an endpoint (160). Several trials have targeted specific aspects of sarcopenia such as muscle function (159) or muscle mass (161, 162). Resistance training increases muscle mass and strength (162). Nutritional interventions have received much attention, especially in

the form of oral nutritional supplements with high protein content and vitamin D (163), or in combinations with exercise (164). The effects of different nutritional interventions have so far been limited (78, 164). For some patients, sarcopenia is caused by specific diseases. In those cases, the best treatment of sarcopenia is treatment of the underlying disease. Examples are medical treatment of heart failure (96) or liver transplantation for patients with end-stage liver disease (165). There is great interest in pharmacologic treatments of sarcopenia due to the potential to prevent functional impairment in aging populations and to reduce the need for institutionalization. Several drugs are undergoing clinical trials in humans, but none are currently approved for the treatment of sarcopenia. Intervention studies of testosterone treatment in older men with low testosterone showed no evidence of effect on walking distance (166), but improved bone mineral density (167). Selective androgen receptor modulators act on androgen receptors in selected tissues and aim to reduce the risk associated with unwanted androgen stimulation. Ghrelin is a hormone that stimulates appetite, increases growth hormone and insulin growth factor. Ghrelin agonists are undergoing trials in humans to treat cancer cachexia (168). Bimagrumab, a monoclonal antibody that is an inhibitor of myostatin, is currently undergoing trials as treatment of sarcopenia (169). ACE inhibitors have shown some promising results in improving physical performance (170).

1.3 Sarcopenia in hip fracture patients

Patients with hip fracture are of special interest in sarcopenia research (171). These patients have many of the characteristics associated with sarcopenia, including older age, female sex, malnutrition, falls and fractures, reduced mobility and impairments in activities of daily living. In persons with sarcopenia the habitual force of skeletal muscle contractions on the skeleton is reduced which leads to weaker bone structure (172). Targeting sarcopenia is a potential mechanism for improving outcomes after hip fracture (173). Patients have lower grip strength and gait speed compared to controls (174). There are several studies on patients with hip fracture examining specific

aspects of the condition of sarcopenia, such as muscle mass, muscle strength or muscle function. There are fewer studies using the newer sarcopenia framework of examining both low muscle mass and reduced muscle function. The prevalence of sarcopenia in hip fracture patients was found to be 12-74% in men and 18-68% in women in 6 studies using the newer definitions of sarcopenia (148, 173, 175-178). Progressive resistance exercise is the main treatment for improving physical performance in patients with hip fracture (38, 179). Nutritional interventions for improving muscle mass in hip fracture patients have been investigated in two recent studies of (177, 178), but with inconclusive results. Testosterone is of interest as treatment for sarcopenia in women with hip fracture, but a Cochrane review of three small intervention studies found insufficient evidence of effect (180). A non-steroidal selective androgen receptor modulator drug has announced promising results of a 12 week phase 2 study in 108 patients with hip fracture, but results have not undergone peer review (181). The myostatin inhibitor Bimagrumab is currently studied in hip fracture patients with results expected in 2018 (182).

2. Aims and hypothesis

This thesis is based on the research project sarcopenia in patients with hip fracture. The aim of this thesis is to investigate sarcopenia as a clinically useful risk factor for adverse outcomes in patients with acute hip fracture. Determining sarcopenia status can aid in identifying vulnerable patients and contribute to personalized medicine. The results are presented in four papers.

- In paper I, we aim to validate bedside measurement of muscle mass, which is necessary for determining sarcopenia status. Our hypothesis is that BIA and anthropometry are valid methods for measuring muscle mass in patients with hip fracture.
- In paper II, our aim is to validate BIA for determining the body composition of patients with recent surgery and who have surgical implants. Our hypothesis is that BIA measurements are not affected by hip fracture and type of surgical implant.
- In paper III, we aim to assess the relevance of sarcopenia in patients with hip fracture by investigating the feasibility of diagnosing sarcopenia at the bedside and the prevalence of sarcopenia. Our hypothesis is that it is feasible to determine sarcopenia, that it is a prevalent condition, and that it is associated with established risk factors for adverse outcomes.
- In paper IV, our aim is to investigate sarcopenia as a risk factor for adverse outcomes after hip fracture. Our hypothesis is that sarcopenia status predicts change in mobility and other adverse outcomes in the year after fracture.

3. Methods

Sarcopenia in patients with hip fracture is an observational, prospective, multicenter study on 282 acute hip fracture patients with one-year follow-up. Table 2 gives an overview of the 4 papers published on the findings of the study. These form the basis of this thesis. Papers I and II included patients from Haraldsplass Deaconess Hospital and Haukeland University Hospital, whereas papers III and IV also included participants from Diakonhjemmet Hospital. In paper I only those who returned for follow-up at three months were used for analysis, while paper II analyzed participants who were assessed in hospital or at follow-up. Papers III and IV used the whole sample of 282 participants.

Table 2: Overview of the four papers of this thesis

Paper	N	Setting	Hypothesis	Principal findings
I	162	3 months after hip fracture at HDS and HUS.	BIA and anthropometry can determine muscle mass.	BIA and anthropometry can identify low muscle mass.
II	203	Hospitalisation and 3-month follow-up at HDS and HUS.	BIA is not affected by surgical implants or surgery.	BIA is not affected by surgical implants but is affected by fracture and surgery.
III	282	Hospitalisation at HDS, HUS and DS.	It is feasible to determine sarcopenia and sarcopenia is common.	Determining sarcopenia was feasible, prevalence was 37% and was associated with age, comorbidities and malnutrition.
IV	282	One-year follow-up at HDS, HUS and DS.	Sarcopenia predicts change in mobility after hip fracture.	Sarcopenia does not predict change in mobility, but reduced mobility, B-ADL and institutionalization or death.

Table 2. N: number of participants. HDS: Haraldsplass Deaconess Hospital. HUS: Haukeland university hospital, DS: Diakonhjemmet hospital. BIA: Bioelectrical impedance analysis. B-ADL: Barthel activities of daily living

3.1.2 Setting

Participants were recruited when in hospital for surgical repair of hip fracture at Haraldsplass Deaconess Hospital, Haukeland University Hospital, Bergen, Norway, or Diakonhjemmet Hospital, Oslo, Norway during 2011-2013. Inclusion criteria were age 65 years and older, able to walk without help from another person before the hip fracture, and able to give informed consent. Permanent residents of nursing homes or patients who had an expected life expectancy of less than three months were excluded. Participants with pacemakers or implanted defibrillators were excluded as BIA can interfere with implanted electrical devices. Bone disease, apart from osteoporosis or

osteomalacia, was also an exclusion criterion. Participants could not suffer from delirium, severe pain, have acute respiratory failure or be in shock at inclusion.

3.1.3 Ethics

All participation was by written, informed consent. Patients were included in the postoperative phase as pain and anxiety is reduced after surgery. Participants received information about the study and were asked to sign the consent form on a subsequent day. In situations where the capacity for consent was in doubt, experienced medical doctors and the rest of the team treating the patients were consulted. Institutional approval was granted from the participating hospitals, the National Hip Fracture Register and the Regional Committee on Medical and Health Research Ethics, REC South East with case number 2011/1322/REK. The study was conducted according to the principles of the Declaration of Helsinki (183).

3.1.4 Data collection

Patients admitted to hospital with suspected hip fracture were screened for inclusion when research staff was present. Some patients were discharged or refused further examinations before all data were collected. We did not record the details of the patients who did not participate in the study. The participants' pre-fracture impairments in activities of daily living were determined by Barthel activities of daily living (B-ADL) (184). Nutritional risk was assessed with the nutritional risk screening (NRS 2002) (185). Serum albumin and 25-OH vitamin D were measured in the fasting state, either pre- or postoperatively. Comorbidities and the ASA score (186) were assessed by chart review, and the Charlson comorbidity index was calculated (187). Information on the number of medications used and any use of supplemental vitamin D was collected at discharge. Length of stay in hospital was collected from the electronic health record. Information on previous hip fracture, type of hip fracture and

surgery was made available from the National Hip Fracture Register. Vital status was supplied by the National Registry.

3.1.5 Muscle mass

Validating BIA and anthropometry for identifying low muscle mass in patients with hip fracture was the topic of paper 1. Table 3 lists the equations for determining ALM by BIA and anthropometry.

Table 3. Appendicular lean mass equations by BIA and anthropometry

First author	BIA equations
Kyle (188)	$-4.211 + (0.267 \times \text{height}^2) / \text{resistance} + 0.095 \times \text{weight} + 1.909 \times \text{sex} - 0.012 \times \text{age} + 0.058 \times \text{reactance}$
Tengvall (189)	$(-24.021 + 0.33 \times \text{height} - 0.031 \times \text{resistance} + 0.083 \times \text{reactance} - (1.58 + 1.58 \times \text{sex}) + 0.046 \times \text{weight}) / 1.19 + 1.65$
Janssen (190)	$(\text{height}^2 / \text{resistance} \times 0.401 + (\text{sex} \times 3.825) + (\text{age} \times -0.071) + 5.102) / 1.19 + 1.65$
Sergi (191)	$-3.964 + 0.227 \times \text{height}^2 / \text{resistance} + 0.095 \times \text{weight} + 1.384 \times \text{sex} + 0.064 \times \text{reactance}$
First author	Anthropometry equations
Villani (192)	$22.28 - 0.069 \times \text{age} + 0.407 \times \text{weight} - 0.807 \times \text{BMI} - 0.222 \times \text{MAC}$
Heymisfield (112)	$(\text{height} \times 0.0264 + (0.0029 \times ((\text{MAC} - \pi \text{TSF})^2 / 4\pi) - (10 \text{ for men, or } 6.5 \text{ for women}))) / 1.19 + 1.65$

Table 3. Sex: Men=1, women=0. Height, centimeters. Weight, kg. BMI: body mass index, kg/m². Resistance and reactance, Ohm. Age, years. MAC: midarm circumference, cm. TSF: triceps skinfold, cm. Height, cm.

Bioelectrical impedance analysis

We studied the validity of BIA for determining body composition in patients with hip fracture in papers I and II. BIA measurements in hospital were performed when the patients had returned to the orthopedic ward after surgery. BIA was measured with the participant supine in a hospital bed by single frequency tetrapolar BIA devices, RJL quantum systems III (RJL systems, USA) and Body impedance analyzer BIA 101 ASE (Akern Srl, Italy). The resistance and reactance to a current of 0.4 or 0.425 milliamperes at a frequency of 50,000 hertz was determined. Electrodes (RJL systems, USA) were placed on the dorsum and wrist of the hand, and at the ankle and dorsum of the foot. Arms and legs were splayed and not in contact with other parts of the body. Rings, bracelets and wristwatches were removed, if possible. Patients were measured first on one half of the body, then immediately afterwards on the other half using a new set of electrodes, by the same operator and using the same BIA device. In total there were four BIA measurements per participant, two measurements per participant in hospital and two at follow-up at three months. Participants were not fasting, and they did not empty their bladder before measurements. All BIA measurements were done by research staff. The decision to measure both sides of the body was by protocol amendment after inclusion had started. For paper I, BIA values were used in equations by Kyle et al (189), Tengvall et al (189), Janssen et al (191) and Sergi et al (191) for predicting muscle mass. See table 3. Results for total body muscle mass by the Tengvall and Janssen equations were converted to ALM by model 1 described by Kim et al (106), taking into consideration intramuscular adipose tissue. Participants at Diakonhjemmet hospital were measured with a different type of BIA device which was not comparable to the BIA devices used in Bergen, and were not analyzed.

Anthropometry

Validation of anthropometry to determine muscle mass was a topic of paper I. Anthropometry was used for diagnosing sarcopenia in paper III and IV. Participants were weighed with light clothes, without shoes. Height was primarily determined using a wall mounted stadiometer. Some of the patients were not able to have their

standing height measured. In these cases, self-reported height or body length measured from heel to crown while lying in bed was measured. If height at baseline was still missing, height measured at follow-up was used. Triceps skinfold and midarm circumference was measured by trained staff. Midarm circumference was measured on the right arm at the mid-point between the acromion and olecranon process with the arm hanging down. Triceps skinfold was measured using a skinfold caliper (Harpenden, Bate International, Great Britain). Measurements of triceps skinfold were repeated until two readings were within 1mm. BMI was calculated. Total body muscle mass by anthropometry Heymsfield was converted to ALM (106).

Dual-energy X-ray absorptiometry

Whole body DXA was the reference method for determining ALM in paper I. Measurements were performed by experienced technicians using one single densitometer (Lunar Prodigy, GE, USA, encore version 13) at an outpatient clinic. The densitometer was calibrated every day and was stable during the measurement period. The in vivo short-term precision for lean mass was <1%. Participants at Diakonhjemmet hospital did not undergo whole body DXA.

3.1.6 Sarcopenia status

Sarcopenia status was determined postoperatively, at follow-up at three months, and was analyzed in papers III and IV. We used the definition of sarcopenia recommend by the EWGSOP (73), but with two important modifications. We used anthropometry to determine low muscle mass, which is not recommended by the EWGSOP for research purposes. Further, for sarcopenia status we used the two categories of not sarcopenia and sarcopenia, instead of the four categories of normal, presarcopenia, sarcopenia and severe sarcopenia. To be categorized as sarcopenic participants had to have low muscle mass and one of either low grip strength or low mobility. Total body muscle mass was estimated by anthropometry by the method of Heymsfield et al (112)

and converted to ALM by model 1 of Kim et al for paper III (106) and model 1 by Kim et al for paper IV (107). The difference between the two models was that intramuscular adipose tissue, set at 0.64kg, was subtracted from ALM for paper IV, but not for paper III. Cut-points for low muscle mass were ALM divided by height squared, $\leq 7.25\text{kg/m}^2$ for men and $\leq 5.67\text{kg/m}^2$ for women, as recommended by the EWGSOP.

Muscle strength

Grip strength was measured with a Jamar dynamometer (Lafayette Instrument, USA). One side was measured three times and immediately afterwards the other side. Grip strength was measured while participants were sitting upright in bed or on a chair. The elbow was flexed with the shoulder and wrist in the neutral position. We accepted a reading of zero if the patient attempted to perform the measurement and followed all aspects of the instruction. There was a brief interval between attempts while the dynamometer was repositioned. The single best value was used. The cut-points for low grip strength was $\leq 30\text{kg}$ for men and $\leq 20\text{kg}$ for women, as recommended by the EWGSOP (73).

The New Mobility Score

Mobility was determined by the New Mobility Score (NMS). The NMS assesses mobility before the fracture by interview. It ranges 0-9; a score of zero indicates that the person is not ambulatory and nine indicates an ability to walk without assistance while shopping (193). See table 4. Low mobility was defined as NMS < 5 , based on the cut-point recommended for predicting mortality after hip fracture (194). The NMS is recommended by AOTrauma and Danish national guidelines for treatment of hip fractures to determine the pre-fracture mobility (195, 196).

Table 4. The New Mobility Score.

	Able to do without difficulty	On their own, but with an aid	Only with someone's help	Not at all, i.e. bed, chair or homebound
Can the patient do their own shopping?	3	2	1	0
Is the patient able to get out of the house?	3	2	1	0
Is the patient able to get about the house?	3	2	1	0

*Table 4: The New Mobility Score, adapted from Parker and Palmer (194).
The three categories are added to create a score 0-9.*

Follow-up at three months

Follow-up at three months was at outpatient clinics. Scheduling of the follow-up appointment was flexible to increase attendance and minimize the inconvenience for participants. Measurements of body composition with DXA, BIA and anthropometry were performed on the same day. Investigators were blind to the results for ALM for the different measurements. Sarcopenia status and B-ADL was determined. Follow-up data at three months were used in paper I, II and IV.

Outcomes at one-year

Outcomes after one year of follow-up were described in paper IV. We did a telephone interview with patients or their care-giver. Telephone interview was chosen to reduce the efforts and costs of acquiring the information for both study investigators and participants. Information on reoperations or second hip fractures was supplied by The Norwegian Hip Fracture Register (46). We collected information on NMS, B-ADL, hospitalizations, reoperation for hip fracture, new fractures, new hip fractures, and becoming a resident of a nursing home. The primary outcome in paper IV was change in mobility, calculated as NMS at one year minus the pre-fracture NMS.

3.1.7 Statistical analyses

A range of different statistical analyses were used in the thesis. Participant characteristics were described with mean values and standard deviation, median values and interquartile range, or counts with percentages. Several versions of IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA), Stata Statistical Software (College Station, TX, USA) and one version of R, 3.3.0 (R foundation for statistical computing, Vienna, Austria) (197) were used for statistical analysis. All analyzes were two-sided and $p \leq 0.05$ was considered significant.

Statistics in paper I

For the four different BIA methods and the two anthropometric methods participants were classified as having low or normal ALM and compared to low or normal ALM by DXA using receiver operating characteristics with area under the curve (AUC) (198). Low ALM was defined as $\leq 7.25 \text{ kg/m}^2$ for men and $\leq 5.67 \text{ kg/m}^2$. The ROCGOLD function in STATA was used to compare the AUC of the different methods. Analysis was stratified by sex and corrected for multiple testing. Sensitivity and specificity for identifying low muscle mass was presented graphically and positive and negative likelihood ratios for each method was determined. ALM by the different methods was analyzed as a continuous variable compared to ALM by DXA by the method of Bland and Altman with mean bias and limit of agreement (LOA) (199). For use in individual patients we decided that the method should be able to identify ALM with a precision within 1kg of that determined by DXA, as a 1kg change in muscle mass is considered clinically relevant (164). For analysis of groups of patients, the mean bias should be as small as possible.

Statistics in paper II

The resistance of the fractured and unfractured hip was analyzed by mean bias with LOA according to the method of Bland and Altman (199). This method was chosen

because we considered the measurements of the fractured and the unfractured side of the body as two alternative methods for determining whole-body muscle mass. We assumed that BIA measurements on the side of the unfractured hip were not affected by the surgery or surgical implants of the fractured hip. We also assumed that any effect of fracture or surgery would be reduced at follow-up compared to while in hospital. Resistance and reactance of the fractured side was compared with unfractured side using paired T-test, in hospital and at follow-up. For determining the influence of surgical implants on resistance and reactance, the difference between the resistance and reactance of the fractured and unfractured hip was analyzed by analysis of variance using three categories of surgical implant, hip screws, compression hip screw and hip arthroplasty.

Statistics in paper III

To determine the feasibility of assessing sarcopenia status we described our problems with gathering data. The association between sarcopenia as dependent variable and the different risk factors as independent variables was analyzed in separate logistic regression analyses with odds ratios and 95% confidence intervals. Analysis was adjusted for age, BMI and sex as predictor variables. Separate analysis was also performed with low muscle mass, low grip strength and low mobility as dependent variables.

Statistics in paper IV

Our primary hypothesis was that sarcopenia status predicted change in NMS as a continuous variable. We also analyzed change in B-ADL. For these analyses we used regression analyses with NMS and B-ADL as dependent variables and sarcopenia status at baseline and age, sex and BMI as predictors. The relationship with age and BMI was modelled with restricted cubic splines with 3 knots, placed at the 10%, 50% and 90% quantiles. For the regression analyses, missing values were imputed using multiple imputation. Based on clinical experience we assumed that a change in NMS of 1 point was clinically significant. In secondary analysis we examined the

association between sarcopenia status and NMS and B-ADL using the same method. For the association between sarcopenia and new clinical fractures, new hip fracture, reoperations, all-cause hospitalization, becoming a resident of a nursing home, and the combined endpoint of nursing home or death we used Fisher's exact test. We also explored the association between the separate components of sarcopenia (muscle mass, grip strength and mobility) with change in mobility and change in B-ADL. The associations were analyzed using regression analysis with muscle mass, grip strength and mobility as continuous variables.

4. Results

This thesis has investigated sarcopenia in a population of community-living, ambulatory and cognitively intact patients with acute hip fractures. We have found that anthropometry and BIA have a moderate ability to identifying patients with low muscle mass. BIA is affected by recent surgery, but not by surgical implants. It is feasible to determine sarcopenia status in acute hip fracture patients and the prevalence of sarcopenia is 37%. Sarcopenia is not associated with change in mobility from prefracture to one year after fracture, but it is associated with impairments in mobility and activities of daily living, institutionalization and mortality.

4.1 Paper I: Identifying patients with low muscle mass

In paper I we showed that bedside methods for determining muscle mass in hip fracture patients have moderate accuracy in identifying a state of low muscle mass. Anthropometry by the Heymsfield method had an AUC of 0.71 in women and 0.64 in men for correctly identifying low muscle mass, and 70% in women and 69% of men participants were correctly classified. The different BIA methods had AUCs ranging 0.66-0.89. The method of determining ALM by anthropometry by Villani et al had poor discriminatory ability with a 95% CI of the AUC which included 0.50, indicating that the method was no more accurate than chance. The magnitude of the LOA when comparing ALM by the different BIA methods ranged 6.0 to 8.3kg in women and 6.9 to 9.4kg in men. The magnitude of the LOA for comparing ALM by anthropometry was 7.6 to 10.2kg in women and 11.5 and 14.5kg in men. The mean ALM of the participants was 14.8kg in women and 20.8kg in men and it is obvious that the precision is insufficient for use in individuals. Mean bias was low for all the different methods in women, ranging -1.8 to -0.8kg, indicating that the methods were suitable for use at a group level. Mean bias varied greatly by the different BIA methods in men, ranging from -4.7 to -0.7 kg. Mean bias by anthropometry in men was low at -0.6kg by

anthropometry Heymsfield and 0.1 by anthropometry Villani. BIA and anthropometry had acceptable precision in assessing ALM in groups.

4.2 Paper II: Influence of fracture and surgical implants on BIA measurements

This paper aimed to answer two questions about the use of BIA in hip fracture patients: 1. Does hip fracture and surgery affect BIA readings? 2. Does surgical implants affect BIA readings? We found a small but statistically and clinically relevant effect of fracture and surgery on resistance on the side of the hip fracture shortly after the fracture. Our proposed solution is to measure the opposite side of the body to the fracture. We found no effect on BIA measurements by the presence of cannulated screws, arthroplasty or dynamic hip screws. BIA can be used in acute hip fracture patients if the side opposite to the fracture is measured and BIA readings are not affected by commonly used surgical implants of the hip.

4.3 Paper III: Feasibility of determining sarcopenia and prevalence of sarcopenia

In paper III, we determined sarcopenia status in 202 out of 282 participants and found that it is feasible to determine sarcopenia status in acute hip fracture patients using anthropometry, grip strength and NMS. We determined sarcopenia status a median of 4 days after surgery. An important source of missing values for sarcopenia status were difficulties in determining height. Prevalence of sarcopenia was 37% and sarcopenia was associated with increasing age, lower BMI, lower serum albumin, using a greater number of medications and a higher ASA score. There were no differences in rates of sarcopenia by sex, but men had a greater prevalence of sex-specific low muscle mass. The findings support the feasibility of determining sarcopenia among patients with hip fracture who were living in the community and are independently mobile before the

fracture. The prevalence of sarcopenia of 37% supports sarcopenia as a relevant risk factor in the population of acute hip fracture patients.

4.4 Paper IV: Sarcopenia status and outcomes at one year

In paper IV we found that having sarcopenia did not predict change in mobility from pre-fracture until one year after hip fracture, or from pre-fracture until three months, or from three months until one year. Sarcopenia was associated with having reduced mobility and more impairments in B-ADL one year after hip fracture with a NMS 5.8 and B-ADL 16.8 among those with sarcopenia at baseline, and NMS 6.8 and B-ADL 18.6 in those without sarcopenia. Having sarcopenia at baseline was associated with a higher likelihood of becoming resident of a nursing home with an odds ratio 3.2 and an odds ratio of 3.6 for the combined endpoint of death or becoming a resident of a nursing home. We recommend that pre-fracture mobility be determined in all hip fracture patients to determine future mobility.

5. Discussion

The purpose of the thesis has been to investigate sarcopenia as a clinically useful risk factor in hip fracture patients. This was done in three steps. The first step was to investigate the validity of bedside methods for determining muscle mass. We have described this in papers I and II. Secondly, we investigated the feasibility of determining sarcopenia in postoperative patients and the prevalence of sarcopenia. These results were presented in paper III. Building on our results from the findings in the previous two steps enabled us to investigate how sarcopenia predicted change in mobility and was associated with outcomes at one year.

5.1 Relevance of sarcopenia in hip fracture patients

Hip fractures, with their great prevalence and large influence on health, are a relevant topic for research. The treatment of hip fracture has improved since 2005 (56), and it is reasonable to assume that further improvement is possible considering that orthogeriatric care and extended physical rehabilitation are not yet routine part of treatment. Many patients with hip fracture suffer from reduced muscle mass and reduced physical function (17, 148, 175, 200). Sarcopenia is a modifiable risk factor that can be prevented and treated with exercise interventions (201). The relevance of sarcopenia status in hip fracture patients is determined by the prevalence of sarcopenia, that it can be diagnosed at the bedside, that it predicts adverse outcomes, and that targeting sarcopenia improves health. This thesis has shown that sarcopenia is a relevant risk factor for adverse outcomes, but it is not known if treating sarcopenia will improve health. Extended rehabilitation is expensive in terms of time, manpower, and motivation. It is reasonable to assume that identifying a group of patients with increased risk of adverse outcomes, such as patients with sarcopenia, can enable better use of resources and personalized medicine.

5.2 Methods

5.2.1 Study design

The aim of this thesis was to investigate sarcopenia in patients with hip fracture and for this purpose an observational study design was the best option. When we planned the study in 2011 there was little information on sarcopenia in hip fracture patients in the published literature, and no information on the feasibility of determining sarcopenia, the validity of the different methods to determine sarcopenia, prevalence of sarcopenia and the association of sarcopenia with outcomes. A case control study, where older persons without hip fracture were assessed for sarcopenia, would have enabled more robust conclusions regarding the prevalence of sarcopenia, but was not possible due to resource constraints.

We decided on a multicenter study design to increase generalizability of the results by reducing the influence of local factors, increase the number of included patients and to increase statistical power to analyze our hypotheses. Further, we aimed to develop ties to other centers treating patients with hip fracture for future collaboration. Inclusion of participants at three hospitals led to less central control of the conduct of the study, and to greater rates of missing values, lower rates of recruitments and loss of information on the patients screened for inclusion but not included. To counteract this loss of control we could have compensated with closer follow-up at each hospital with weekly visits and greater use of research nurses, but we did not have the necessary resources available.

We chose follow-up at three months on the assumption that most of the participants would have returned to their own homes and had regained sufficient mobility to attend at that time. Follow-up at one-year was chosen as tradeoff between participants regaining most of the lost mobility after hip fracture, and to minimize missing values

due to death and withdrawals. The rate of death is greatest in the weeks after hip fracture (25), whereas mobility plateaus at one year (36).

5.2.2 Population

Generalizability of results is a major concern of any study. Our study had wide inclusion criteria and recruited participants at three centers. We included only participants able to give informed consent, partly because we found it ethically challenging to recruit patients for a study where there were few benefits for the participants. We included patients older than 65 years to focus on the older population. There is reason to believe that younger patients are different from older patients, with a greater prevalence single disease effects leading to falls and fractures. We chose not to include residents of nursing homes. Older persons living in nursing homes in Norway have a prevalence of dementia of more than 80% (202) and would generally not have the capacity for consent. They would also have more difficulties in attending follow-up examinations. Some research indicates that patients without the capacity for consent receive less benefit from rehabilitation interventions (62).

We included only a minority of all the patients who were operated on for hip fracture at the participating hospitals during the period of inclusion. The number of patients with hip fracture operated on during the period of inclusion was 1,592, of which 282 were included. This is a major limitation of our study and reduces the generalizability of our results. It would have been useful with more information about the participants who weren't eligible or did not consent to participation, but we failed to record this information. The Regional Committee on Medical and Health Research Ethics requested that participants be given information on the first day and to sign the consent on a subsequent day. The extra time was deemed necessary for the patients to consider whether to participate. This unusual process of obtaining consent probably reduced the number of patients included. Some patients were discharged home before the process was completed, and some patients were never screened for inclusion because research

staff were absent from the wards. Even taking these limitations into consideration, the included population was old, suffered from mobility impairments, impairments in activities of daily living, were frequently hospitalized, became institutionalized, experienced fractures, reoperations and mortality during the follow-up. When we compare the age and ASA score of the participants in the present study with all patients in the Norwegian National Hip Fracture Register we find similar values. Age was 79 years in the study and 80 years in the register, ASA score was 2.5 in the study and 2.7 in the register (26). The sample size of 282 participants compares favorably to the other current studies on sarcopenia in patients with hip fracture. See table 5 for an overview of recent studies. For paper I we included 162 patients of which 43 men were available for analysis stratified by sex. When comparing 5 different methods for identifying low muscle mass a sample of 43 men was insufficient to reach firm conclusions. We believe the results of this thesis are valid for older hip fracture patients living in their own home, able to walk without assistance and without cognitive impairment.

5.2.3 Papers I and II: validating bedside methods for determining muscle mass

The topic for papers I and II was validating bedside measures of body composition. We were unable to measure participants by DXA during hospitalization for several reasons: patients were relatively immobile, Haraldsplass Deaconess Hospital did not have a DXA machine, the DXA machine at Haukeland University Hospital was in a separate building from the orthopaedic ward and the treating clinicians were worried that trying to measure body composition by DXA might lead to delays in discharge from hospital. The DXA machine at Haukeland University Hospital was a Lunar Prodigy whereas it was a Hologic Discovery at Diakonhjemmet Hospital, and DXA machines from different manufacturers are poorly cross-validated. MRI or CT would have been more precise in determining ALM and would also enable assessment intramuscular adipose tissue but were not available due to cost and the effort demanded of the participants. We decided not to use the equation by Lee et al for

determining muscle mass. The Lee equation is based on height, weight, sex, race and age and we were interested in estimates of muscle mass that could measure change in muscle mass beyond measuring change in weight (113). The Heymsfield method for determining total body skeletal muscle had the disadvantage that it was necessary to measure triceps skinfold, which is considered technically difficult (112). An advantage of the Heymsfield method is that it is independent of weight and age. We found that BIA or anthropometry have insufficient precision to determine muscle mass as a continuous variable at the individual level, as evidenced by the wide LOA by the Bland-Altman analyses. This indicates that anthropometry and BIA are unable to determine precise ALM, to monitor changes in ALM in interventions studies or during rehabilitation. We did find an acceptable ability to identify low ALM with the different BIA methods with AUC ranging 0.66-0.89 for the different prediction equations and an AUC of 0.64 for women and 0.72 for men for anthropometry Heymsfield. We did not have sufficient statistical power to determine the single best method to identify low muscle mass due to the limited number of participants, because analysis was stratified by sex and due to correcting for multiple testing. It was necessary to stratify by sex because men are substantially different from women. They have greater muscle mass, are younger and suffer higher rates of adverse outcomes compared to women. Correction for multiple testing was necessary since we compared 6 different methods, but an option would have been to investigate fewer methods.

The aim of paper II was to examine the validity of BIA in acute hip fracture patients by investigating the effect of surgery and surgical implants on BIA measurements. We decided to analyze the effect of surgical implants on BIA measurements by dividing the surgical implants into three categories based on the mass of the implant and their position in relation to muscle and bone. The categories were cannulated screws, compression hip screws and hip arthroplasty. We presented the individual data points in scatterplots to more clearly show the distribution of measurements including outliers and the return to the mean from baseline to follow-up. We could possibly have increased the precision of the BIA analysis by having the participants fasting, resting in bed for 5 minutes before testing, having empty bladders and ensuring euvolemia.

We believe that our results are valid and robust to potential inaccuracies in BIA measurements, since we used each person's unfractured hip as control. We also consider our approach to performing BIA measurements a good balance between being feasible in clinical practice and adhering to recommendations for optimal measurements.

5.2.4 Papers III and IV: Sarcopenia in patients with hip fracture

The aims of papers III and IV were to determine the feasibility of determining sarcopenia in acute hip fracture patients and investigate the relevance of sarcopenia as a risk factor. We determined sarcopenia status in 202 of 282 participants. It was challenging to determine height and weight of the participants, as other studies on patients with hip fracture have found (30). For 52 participants with missing values for height determined during the hospital stay, we used height determined at follow-up. Determining height is necessary for identifying low muscle mass and diagnosing sarcopenia. Other studies on sarcopenia in patients with acute hip fracture have used supine height (177, 178), the length of the ulnar bone (148) and knee height (203) to estimate standing height. We reduced the problem of assessing height by using alternative methods, primarily self-reported height or supine height.

We had high rates of missing values in the study. To gather as much information as possible about the participants, and to reduce the number of missing values we had a clear sequence and priority for the data collection. First; consent to participate, second; information about pre-fracture mobility, third; muscle mass by BIA and anthropometry, fourth; grip strength, and finally, all other variables. For the follow-up examination at three months we aimed to increase the attendance rate by being flexible in scheduling. In paper IV, we used multiple imputation in cases with missing values for the variables used in regression analysis. Imputation of missing values improved the validity of our analysis and generalizability of the results compared to using only complete cases. Analysis limited to complete cases reduces statistical power,

especially in multivariable analysis. Complete case analysis, also known as listwise deletion, limits the results of analysis to the part of the population without missing values, or requires that missing values are missing completely at random. An assumption of imputation of missing values is that missing values can be estimated by the pattern of missing values or other information in the dataset. Our results were similar in complete case analysis and when analysed with imputation of missing values, which indicates that our results were robust to the assumptions of both. This supports our findings of no effect of sarcopenia on change in NMS and B-ADL.

Considerations regarding the diagnosis of sarcopenia

There is no established consensus for diagnosing sarcopenia. We had to consider a broad range of options when deciding on how to define sarcopenia. For this research project we decided on the EWGSOP definition based on the authority of the group, and because it broadened the criteria for sarcopenia to include muscle strength and function in addition to muscle mass. The EWGSOP recommends several alternative definitions of low muscle mass such as muscle mass normalized for body weight or body weight and with different cut-points for low muscle mass (77). Muscle mass adjusted for body weight has been criticized for disproportionately classifying obese patients as sarcopenic, which is at odds with the beneficial effects of obesity on mortality in older persons (204). The FNIH sarcopenia project recommendations of ALM/BMI were not published at the time we wrote the protocol, and the changes did not seem sufficiently substantial to warrant a change in protocol. The different recommended cut-points for low muscle mass by the EWGSOP normalized for height squared were similar, ranging from 5.5kg/m² to 5.67kg/m² for women and 7.23 to 7.26 kg/m² for men, and for practical purpose the differences were small (73).

The EWGSOP recommends using four categories of sarcopenia, normal, presarcopenia, sarcopenia, and severe sarcopenia. We decided against using the four categories because we were uncertain about the added value of including a presarcopenia category. Di Monaco et al found that the group with presarcopenia had

better outcomes for improvement in the B-ADL, compared to the group categorized as normal (176). One possible explanation is that grip strength is a stronger indicator of adverse outcomes than muscle mass and that the patients with presarcopenia, by definition, have normal grip strength. Using two categories increased our sample size, and is the approach most commonly used in studies on sarcopenia (148, 205). The EWGSOP does not recommend anthropometry for determining muscle mass in research, but it is well established in clinical practice. DXA was not an option for determining ALM in this study. We did not have financing for whole body DXA at Diakonhjemmet Hospital, and we did not believe that patients who had recently undergone surgery would be able to undergo DXA due to pain and immobility. We chose anthropometry for identifying low muscle mass because our results in paper I indicated that anthropometry had an acceptable discriminatory ability, and because this enabled us to determine sarcopenia status using the same techniques at all three hospitals. BIA was not available at Diakonhjemmet hospital. There are quick screening tools for sarcopenia (206), which could facilitate identifying acute hip fracture patients with sarcopenia. Goodman et al have developed a screening tool using age, sex and BMI to identify persons at risk of having low muscle mass (207) and Malmstrom et al have developed the SARC-F to identify patients with sarcopenia (208). The SARC-F was not published until after enrolment was finished, and so was not an option for us.

We decided to use grip strength to determine low muscle strength, as this is the most widely used and studied measure of muscle strength. There are many different protocols for how maximal grip strength should be determined (110) and these differences in protocol can be clinically relevant (209). The Southampton protocol aims to standardize test conditions for grip strength (127). We adhered to most of the recommendations, with two exceptions. We accepted measurements while the patient was in bed instead of in a chair and we did not alternate hands for each attempt. We encountered no difficulties in measuring grip strength, and consider it a useful tool in determining strength at the bedside.

We chose the NMS as our measure of physical performance because we assumed that many of the participants would be unable to perform objective tests of physical performance, and to reduce the burden of participation of participants and investigators. The NMS is not one of the alternatives recommended by the EWGSOP, and the FNIH sarcopenia project only requires grip strength and muscle mass. Options recommended by the EWGSOP are all objectively measured tests of physical performance such as the Short Physical Performance Battery, usual gait speed, Timed get-up-and-go test and stair climb power test (73). Other studies on hip fracture patients where sarcopenia status is determined shortly after fracture, have not measured physical performance (200). A group of experts sponsored by the AOTrauma network recommends measuring the NMS at pre-fracture, at 90 days and at one-year (195). No studies have recommended a cut-point for low NMS in the context of sarcopenia, but $NMS < 5$ indicates increased mortality risk (194). A pre-fracture $NMS < 6$ was associated with objectively measured physical function before discharge from hospital (210), having a reduced mobility at 6 months, or needing assistance in activities of daily living (211). The NMS has been used as an endpoint and repeated measure in intervention trials (212). It has a high interrater reliability (213). We found the NMS intuitive, easy to administer, acceptable for use by both investigators and patients, and easy to administer both for face-to-face and by phone interviews. There was a ceiling effect with more than half of our participants scoring the maximal NMS 9 before the fracture and we found the NMS to be a suboptimal tool for measuring rehabilitation because of the distribution of the scores (214). It is possible that alternative measurement scales developed for hospitalized older patients such as the cumulated ambulation score (215) or the de Morton Mobility index (216) could have been better at determining change in mobility than the NMS.

Participants

We determined if participants were very ill during examination and if so measurements were postponed until patients recovered. It would have been informative if we recorded vital signs such as alertness, respiratory rate, pulse, blood pressure and temperature in order to assess the feasibility of determining sarcopenia in medically unstable patients, and how assessment of grip strength is changed in situations with abnormal vital signs.

Sarcopenia is a predictor of falls (157). A detailed assessment of falls among our participants would have been useful and we could have contributed to insights into the relationship between sarcopenia and risk of falling in a high-risk population. We decided against recording falls as studies have shown that close follow up is necessary for accurate fall surveillance (217). We aimed to determine pre-fracture cognitive status with the IQCODE (218), but had trouble collecting the information from the next of kin, and were unable to use cognitive status in analysis. Smoking and harmful patterns of alcohol intake are associated with sarcopenia and hip fracture (86, 219-222). We did not consider smoking or alcohol use as predictors of sarcopenia or mobility but would want to consider it in a future study. Excess rates of smoking and harmful alcohol intake are possible explanations for why male hip fracture patients have worse outcomes compared to female.

We did not estimate the effect of sarcopenia on length of hospital stay since we consider this an outcome that is sensitive to confounding and that has an unclear relationship to sarcopenia. Most of the participants in our study were discharged to skilled nursing homes for rehabilitation lasting 2-4 weeks before being discharged to their own home. The median length of hospital stay was 6 days for those without sarcopenia and 7.5 days for those with sarcopenia. A small minority of participants were discharged to their own home, and some were discharged to hospital-based rehabilitation facilities. Short and long hospital stays can indicate both successful and

failed rehabilitation. We did not investigate the relationship between intensity of rehabilitation and outcome, which is a potential confounder of the relationship between sarcopenia and outcomes.

5.3 Comparison with other studies

5.3.1 Bedside methods for determining muscle mass in patients with hip fracture

Villani et al investigated anthropometric assessment of total body muscle mass using anthropometry by the Heymsfield method with DXA as the reference method 2 weeks, 6 months and 12 months after hip fracture (192). They found a poor precision with a magnitude of the LOA of 24kg at 2 weeks, 12kg at 6 months and 13kg at one year. The magnitude of the LOA found by Villani et al was comparable to what we found, at 10kg for women and 15kg in men. Villani et al did not investigate the ability of anthropometry to identify low muscle mass and did not stratify his analysis by sex. In a subsequent paper Villani et al proposed a different equation for ALM by anthropometry, using a development and a validation cohort of patients with hip fracture (203). They found a magnitude of the LOA of 10 kg in the validation cohort. We investigated the precision of this equation in paper I and found a LOA of 8kg in women and 11.5kg in men, which is a comparable result. We conclude that our results for the precision of anthropometry in determining muscle mass in patients with hip fracture are comparable to the two Australian studies.

We are not aware of any study on single frequency BIA to determine muscle mass in patients with hip fracture, but one study by Villani et al using multifrequency BIA (192). In a study on single frequency BIA compared to DXA in hospitalized older persons with a range of illnesses, the magnitude of the LOA of BIA compared to DXA for total body muscle mass was 7kg for BIA Tengvall, 6kg for BIA Kyle and 9kg for

BIA Janssen. Outliers corresponding to 7% of the participants were removed from the dataset (223). The results were of a comparable precision to what we found in our study where the magnitude of the LOA ranged 6-10kg for ALM. In general, results from the research describing the development of BIA derived prediction equations for ALM has greater precision than subsequent validation studies. We conclude that our results on the validity of BIA to determine muscle mass are in line with other research, with the caveat that we are not aware of any studies validating BIA or anthropometry to identify low muscle mass as a dichotomous outcome.

The results from paper II are original and difficult to compare to previous research as our approach of using one half of the body as the control of the other side has not been investigated before. We have not identified previous research on the influence of fracture or surgical implants on BIA readings.

5.3.2 Other studies on sarcopenia in patients with hip fracture

We are aware of 6 previous studies on patients with hip fracture using both low muscle mass and low muscle strength or muscle function to diagnose sarcopenia (148, 173, 175-178). The studies were heterogeneous in setting, methods used, and outcomes investigated. Some of the details of the studies are summarized in table 5. Patients were included during the acute hospital stay in 2 studies, during in-hospital rehabilitation in one study, and during post-acute rehabilitation in 3 studies. Patients had their sarcopenia status determined preoperatively in the study by Gonzalez-Montalvo et al, and postoperatively ranging from a week to up to 52 days after the fracture in the other 5 studies. Sample size varied from 79 to 479 with a follow-up period varying from discharge from hospital to 12 months. Two studies, by Flodin et al and Malafarina et al, were intervention studies examining the effect of nutritional supplements on muscle mass, whereas the other studies were observational. Determination of muscle mass was by DXA in 4 studies and BIA in 2 studies, and all 6

studies used different cut-points for low muscle mass. The studies using BIA to determine muscle mass measured the unfractured side, and thus avoided the problem of the influence of the fracture on BIA measurements. All 6 studies used grip strength to determine strength, but with 4 different cut-points for low grip strength. Only the study by Malafarina et al measured of physical function (178).

The prevalence of sarcopenia varied from 17% to 72%. Prevalence of presarcopenia in two studies varied from 12% to 21% (175, 176). Flodin et al found that the prevalence of sarcopenia increased from 24% in hospital to 29% one year after the hip fracture (177). Reporting of the association between sarcopenia, key demographics and risk factors was inconsistent across studies. Landi et al and Gonzalez-Montalvo et al reported an increasing prevalence of sarcopenia with age. Ho et al and Landi et al found a higher prevalence of sarcopenia in men compared to women, whereas Gonzalez-Montalvo et al found no association. Di Monaco et al included only women.

Sarcopenia was associated with low BMI in three studies, there was no association in the fourth, while two studies did not report results. There was no association between malnutrition and sarcopenia in the studies by Landi et al and in Gonzalez-Montalvo et al when using serum albumin, vitamin D and the Mini Nutritional Assessment. The relationship between sarcopenia and comorbidities varied by study and how comorbidities were assessed. Di Monaco et al found no association between sarcopenia and number of concomitant diseases or number of medications. Gonzalez-Montalvo et al found no association between sarcopenia and ASA score. Landi found an association between sarcopenia and increasing comorbidities using the Charlson comorbidity index, but not for number of medications. The association between sarcopenia and activities of daily living before the hip fracture was assessed in three studies, and no difference was found. Landi et al found a greater improvement in B-ADL after rehabilitation in participants without sarcopenia.

Table 5. Recent studies on sarcopenia in patients with hip fracture.

First author	Country	N	Centers	Sarcopenia prevalence	Follow-up
Di Monaco (176)	Italy	138	1	58%	Discharge
Flodin (177)	Sweden	79	4	21%	1 year
Gonzalez-Montalvo (148)	Spain	479	1	17%	Discharge
Ho (175)	China	239	1	W: 68% M: 74%	Discharge
Landi (200)	Italy	127	1	34%	3 months
Malafarina (178)	Spain	107	2	72%	Discharge
Steihaug (224)	Norway	282	3	37%	1 year

Table 5. N: number of participants in the study. M: men. W: women.

In summary, our results for the prevalence and associations of sarcopenia are within the broad range of results from other studies, but the studies are not directly comparable due to the inclusion of different groups of patients and different methods for determining sarcopenia status. It is challenging to generalize results from these studies. The field of sarcopenia research needs larger studies, consensus on how to diagnose sarcopenia and harmonization of the reporting of results.

6. Conclusions and implications

This thesis has expanded the knowledge about sarcopenia to patients with hip fracture. We have validated BIA and anthropometry to identify patients with low muscle mass in acute hip fracture patients, improving the feasibility of diagnosing sarcopenia at the bedside. We have found that it is feasible to determine sarcopenia using anthropometry, grip strength and self-reported mobility. Further, we have found a prevalence of sarcopenia of 37% and that sarcopenia is associated with age, comorbidities and malnutrition. We found no evidence that sarcopenia predicts change in mobility in the year after hip fracture, but sarcopenia is associated with having reduced mobility, and becoming a resident of a nursing home or death.

6.1 Implications for clinical practice

This is the first validation study on the use of single frequency BIA in acute hip fracture patients. Our findings support using BIA for identifying persons with low muscle mass. BIA is not affected by surgical implants, and can be used postoperatively if the contralateral side to the fracture is measured. A large part of the older population live with surgical implants, and our findings support the use of BIA to determine body composition in this group. Anthropometry is a valid screening tool for low muscle mass, with a precision comparable to BIA. We recommend BIA or anthropometry as bedside screening tools for identifying patients with low muscle mass. DXA should be reserved for patients able to get out of bed, and for cases where the improved precision will have clinical consequences. We have found that it is feasible to determine sarcopenia status in patients with hip fracture. Sarcopenia is a risk factor for having reduced mobility and impairments in activities of daily living, which are outcomes are important to patients. We recommend determining sarcopenia status to identify at risk patients. All patients with hip fracture should have their pre-fracture mobility assessed as an indicator of future adverse outcomes, and as a benchmark for successful

rehabilitation. Pre-fracture mobility was strongly associated with poor mobility at one year and was easy to determine with the NMS.

6.2 Implications for further research

The results presented in this thesis enable future research on sarcopenia in acutely ill and frail older persons. Patients with hip fracture patients are heterogenous (225), and for future intervention studies on sarcopenia, nutrition or physical performance we recommend that potential participants are screened for low muscle mass by BIA or anthropometry. Anthropometry or BIA can also be used for determining muscle mass in groups of patients. Our results support the use of BIA to determine body composition in populations with a significant prevalence of surgical implants, such as in population studies including older persons or patients with hip fracture. There is continuing uncertainty about the best method of determining sarcopenia, including definition, measurement techniques and cut-points. Further research on the validity of the diagnosis of sarcopenia is necessary to harmonize methods across studies, improve generalizability, and enable changes in clinical practice to improve the health of patients. Determining the height of patients with acute hip fracture is challenging, and more research is necessary to validate measures of body size in patients that are immobile, confused, and with reduced standing height due to fractures of the vertebral column. Surrogate measurements of standing height such as self-reported height have poor precision (226) which can lead to misclassifications of low muscle mass. An ideal bedside determination of body composition should be independent of exact height, and future research on how to do this would be useful. Anthropometry and BIA to determine muscle mass have less than ideal precision. DXA might not be the optimal method for determining muscle mass, and future studies should examine alternatives such as ultrasound, serum biomarkers or imaging such as CT. Future research on sarcopenia could benefit by using objective tests of physical performance that can be used for repeated measurements. A special challenge in testing of physical performance in patients with hip fracture is to avoid floor and ceiling effects. Some

patients are unable to walk at all, and some go hiking in the mountains. As an outcome measure, the NMS is suboptimal because of a ceiling effect. Alternatives are the cumulated ambulation score (215) and De Morton Mobility Index (216). We found that follow-up by phone interview was acceptable to patients, low-cost and easy to do, and recommend it for future research. Future studies need a combination of larger sample sizes and more precise determination of sarcopenia status. Special attention to male hip fracture patients is warranted in the light of their poorer outcomes and high frequency of low muscle mass. Intervention studies aiming to prevent hip fractures or improve outcomes after hip fracture by targeting sarcopenia are needed.

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PAPER II

*Bones, Blood and Steel: How Bioelectrical
Impedance Analysis is affected by Hip Fracture
and Surgical Implants.*

Bones, blood and steel: How bioelectrical impedance analysis is affected by hip fracture and surgical implants

Ole Martin Steihaug^{1,5}, Bård Bogen^{1,2}, Målfrid Holen Kristoffersen³ and Anette Hylen Ranhoff^{1,4}

1. Haraldsplass Deaconess Hospital, Bergen, Norway
2. Bergen University College, Bergen, Norway
3. Department of Orthopedics, Haukeland University Hospital, Bergen, Norway
4. Institute of Clinical Science, University of Bergen, Bergen, Norway
5. E-mail any correspondence to: osteihaug@gmail.com (OMS)

Abstract

Introduction: Bioelectrical impedance analysis (BIA) is in wide-spread use, but there is uncertainty about its validity in patients with metal implants or after acute hip fracture and surgery. We aimed to investigate the use of single frequency tetrapolar BIA in patients with hip fracture by answering the following questions: 1) Are BIA measurements affected by recent hip fracture and surgical repair? 2) Are BIA measurements affected by the presence of metal implants used in hip fracture surgery?

Setting: Two hospitals in Bergen, Norway.

Participants: A convenience sample of 203 acute hip fracture patients.

Methods: Participants had their body composition measured by single frequency, tetrapolar BIA on the fractured and unfractured side of the body in the immediate postoperative period and at follow-up three months after hip fracture. Measurements from fractured and unfractured side and measurements in hospital and at follow-up were compared. BIA readings for hips treated with cannulated screws, compression hip screw and hip arthroplasty were compared.

Results: Resistance was lower on the side of the fractured hip compared to the unfractured side postoperatively, but not at follow-up. BIA readings did not differ by type of surgical implant.

Conclusion: Recent fracture and surgery influences single frequency tetrapolar BIA resistance. The presence of surgical implants in the hip do not affect BIA measurements. If BIA is used in acute hip fracture patients, the contralateral side to the fracture should be measured.

Keywords: Hip fracture, surgical implants, bioelectrical impedance analysis

Introduction

Bioelectrical impedance analysis (BIA) is a popular tool for determining body composition (1). BIA is painless, requires minimal mobility by the person being measured, is portable and does not expose users to radiation. It is found in a range of inexpensive consumer-targeted devices such as bathroom scales, it is used by healthcare workers to determine the health and nutritional status of persons (2) and it is in use in large population based studies of body composition (3). BIA has been validated in comparison with other methods of determining body composition such as Dual Energy x-ray absorptiometry (DXA), underwater weighing and Magnetic Resonance Imaging (4, 5). BIA has been validated prospectively as a method to determine elevated risk associated with adverse body composition profiles (6). We have previously used data from this study to validate BIA for determining muscle mass in hip fracture patients (7). Patients with acute hip fracture often have difficulty in walking and getting on to the examination table of a DXA, CT or MRI machine. BIA could be a valuable tool to investigate body composition in acute hip fracture patients. There are still concerns that BIA is not sufficiently validated since BIA is

influenced by health status and should be validated separately in each population (8-11).

Many older persons live with surgical implants. It has been estimated that in the population aged 50+ in the UK there is a lifetime risk of 7-12% for receiving a total hip arthroplasty and 8-11% for total knee replacement (12). The validity of BIA to determine body composition in individuals with surgical implants is not determined, but is widely considered to be problematical (13, 14).

When the proximal femur is fractured, the tension of surrounding tendons and muscle will often lead to dislocation of the fracture ends, which prevents skeletal healing. Surgical treatment of hip fracture involves surgical implants to fix the ends of the femur in their anatomical correct position to enable healing. There is a multitude of different surgical implants used for hip fracture repair, but the implants most commonly used can be categorized in three broad categories: hemiarthroplasty and total hip arthroplasty, cannulated screws and hip compression screws (Fig. 1 and 2).

Fracture and surgery are associated with discontinuities of the tissue spaces and edema. The surgical implants are mainly made of metals such as steel, titanium, cobalt and chromium with use of other materials such as ceramics, hydroxyapatites and polyethylenes. These changes can potentially increase or decrease the electrical conductance, and it is difficult to predict how they will affect BIA measurements. If BIA is to be useful in the large group of acute hip fracture patients, or other patient groups undergoing surgery, it is important to determine the influence of fracture, surgery and surgical implants on BIA readings. The aim of this study is to answer the following research questions: 1) Are BIA measurements affected by recent fracture and surgical repair? 2) Are BIA measurements affected by the presence of metal implants used in hip fracture surgery?



Photo: Ole Martin Steihaug.

Figure 1: Surgical implants used for hip fracture repair. From left: hemiarthroplasty of the hip, two cannulated screws and a compression hip screw.



Figure 3: Operation methods for hip fractures. Radiograms of different type of implants:

- a. Osteosynthesis with 2 screws
- b. Osteosynthesis with hip compression screw
- c. Osteosynthesis with hip compression screw with lateral support plate
- d. Osteosynthesis with intramedullary nail
- e. Hemiarthroplasty
- f. Total hip arthroplasty

Fig. 2: Plain film X-rays of hip fractures treated with different surgical implants. From Gjertsen (15). Reproduced with permission.

Methods

Patients admitted to hospital with suspected hip fracture were screened for inclusion in the study when the research staff was present on the hospital wards. Participants had to undergo surgical repair of acute hip fracture and be aged ≥ 65 years, be ambulatory before the fracture, give informed consent, have an estimated remaining life expectancy of >3 months and not have any disease of bone apart from osteoporosis or osteomalacia. Participants could not suffer from delirium, severe pain, have acute respiratory failure or be in shock at inclusion, but could develop these after inclusion. Participants were excluded if they had pacemakers or implanted defibrillators since these could be affected by BIA measurements. Patients could have preexisting surgical implants. Patients who were permanent residents of skilled nursing homes were not eligible for inclusion.

Anthropometry

Patients were weighed with indoor clothing. Height was primarily determined by wall mounted stadiometer. Some of the patients measured in hospital were not able to have their standing height measured. In these cases, self-reported height or length in bed was measured. Length in bed was measured while supine in a hospital bed, measured from heel to crown. Weight was determined by the available scale, often a chair-weight while in hospital.

Bioelectrical impedance analysis

BIA measurements in hospital were performed after hip fracture surgery when the patients had returned to the orthopedic ward from the recovery ward. The BIA resistance

and reactance (ohms) was obtained using single frequency tetrapolar BIA (RJL quantum systems III, RJL systems, USA) with an operating frequency of 50 kHz at 425 μ A, and at 400 μ A and 50 kHz (Body impedance analyzer BIA 101 ASE, Akern Srl, Italy). Electrodes (RJL systems, USA) were placed on the skin at the wrist and ankle with participant supine in a hospital bed. The Quantum systems III was calibrated before measurements. Arms and legs were slightly spread so that they were not in contact with other parts of the body. The skin was not cleaned before applying the electrodes unless it was visibly or palpably dirty. Rings, bracelets and wristwatches were removed, if possible. Patients were not fasting and there was no systematic bladder voiding. Patients were measured first on one half of the body, then immediately afterwards on the other half using a new set of electrodes and by the same operator and using the same BIA device. All BIA measurements were performed by research nurses or the study physicians (MHK, OMS). We limited the sample to participants who had BIA readings from both fractured and unfractured side and did not have surgical implants in the opposite hip. All measurements were performed indoors with stable humidity and temperature between readings. The decision to measure both sides of the body was by protocol amendment after inclusion had started.

Follow-up

Participants were invited for a follow-up examination three months after admission to hospital. On the same day patients were measured by whole body DXA, BIA and anthropometry. Scheduling of the follow-up appointment was flexible to increase attendance and minimize the inconvenience for participants.

Statistics

The resistance of the fractured and unfractured hip was analyzed by mean difference with limits of agreement according to the method of Bland and Altman (16). The Bland-Altman methods was chosen because we considered the measurements of the fractured and the unfractured side of the body two alternative methods for determining whole-body muscle mass. We assumed that BIA measurements on the side of the unfractured hip were not affected by the surgery or surgical implants of the fractured hip. We also assumed that any effect of fracture or surgery would be reduced at follow-up compared to while in hospital. Participants with pre-existing surgical implants in the unfractured hip were excluded from analysis. Resistance and reactance of the fractured side was compared with the unfractured side using paired T-test, in hospital and at follow-up, for a total of four comparisons. For determining the influence of surgical implants on resistance and reactance, the difference between the resistance and reactance of the fractured and unfractured hip was analyzed

by analysis of variance using category of surgical implant. The categories were hip screws, compression hip screw and hip arthroplasty. The arthroplasty category constituted both hip hemiarthroplasty and total hip arthroplasty. $P \leq 0.05$ was considered statistically significant. Analysis was by Stata Statistical Software: Release 14. StataCorp LP, USA.

Ethics

The research was conducted according to the declaration of Helsinki. Participants were given written and verbal information about the study on the first day and were asked to sign the consent form on a subsequent day. This enabled time for deliberation and to consult their next of kin. Participants were included when they had been mobilized to sitting upright and with adequate pain relief. In situations where the capacity for consent was in doubt, experienced medical doctors and the rest of the team treating the patients were consulted.

Results

Table 1: Characteristics of the participants.

Age, years (SD)	80	(8)
Female, n (%)	151	(76)
Right sided fracture, n (%)	109	(54)
Type of surgical implant, n (%)		
Cannulated screws	44	(22)
Hemiarthroplasty	62	(31)
Hip compression screw	83	(41)
Total hip arthroplasty	8	(4)
Femoral nail	6	(3)

	In hospital			At follow-up		
Height (SD), cm	166	(10)	$n=136$	164	(9)	$n=162$
Weight (SD), kg	66	(16)	$n=136$	64	(14)	$n=162$
Fractured hip						
Resistance (SD), Ohm	491	(95)	$n=134$	555	(95)	$n=157$
Reactance (SD), Ohm	46	(31)	$n=134$	49	(13)	$n=157$
Unfractured hip						
Resistance (SD), Ohm	527	(99)	$n=131$	552	(89)	$n=158$
Reactance (SD), Ohm	53	(51)	$n=131$	53	(23)	$n=158$

Table 2: Pairwise comparisons of BIA readings on fractured and unfractured hips.

	Fractured		Unfractured		P-value	N
Resistance						
Hospital	496	(98)	527	(101)	0.0007	81
Follow-up	553	(98)	550	(92)	0.4	134
Reactance						
Hospital	45	(20)	56	(64)	0.068	81
Follow-up	49	(14)	52	(23)	0.061	134

During the period of inclusion 843 patients were operated on for hip fracture, 203 were included and 163 returned for follow-up. All participants were Caucasian. BIA was performed at a median of 5 (IQR 4-7) days after hip fracture, which was a median 4 (IQR 2-5) days after surgery.

The number of days from admission to follow-up was a median 112 days (IQR 98-133).

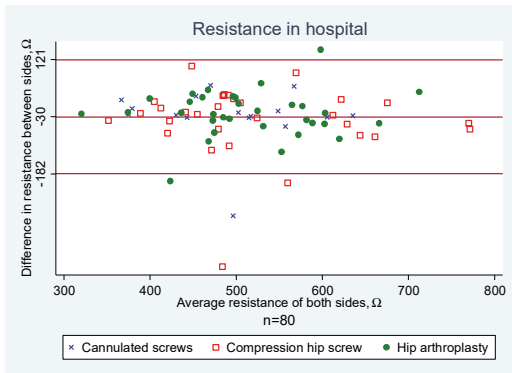


Fig. 3: Bland-Altman plot of difference in resistance between fractured and unfractured hip postoperatively after hip fracture. Red lines are the mean, upper and lower limits of agreement (mean bias ± 1.96 standard deviations).

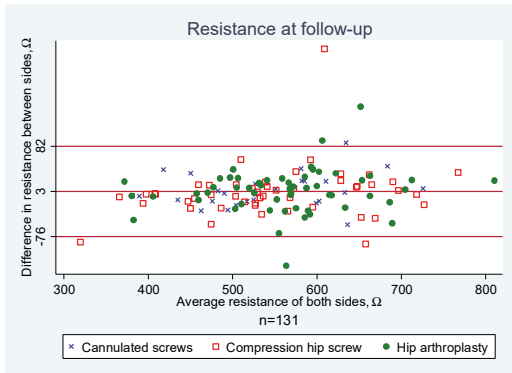


Fig. 4: Bland-Altman plot of difference in resistance between fractured and unfractured hip 3 months after hip fracture. Red lines are the mean, upper and lower limits of agreement (mean bias ± 1.96 standard deviations).

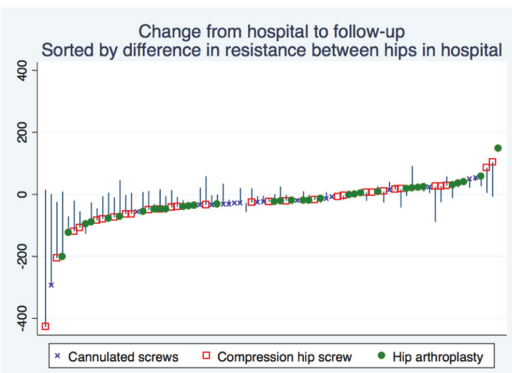


Fig. 5: Change in difference between fractured and unfractured hip from hospital to follow-up. Symbols indicates type of surgical implant and difference between fractured and unfractured hip in hospital. The vertical line indicates the magnitude of the change in difference between fractured and unfractured hip from hospital to follow-up.

In hospital, resistance on the side of the body with the fractured hip was lower than the side with the unfractured hip, 496 (SD 98) ohm vs 527 (SD 101) ohm, $P=0.0007$. Table 2. The limit of agreement was wider in hospital compared to at follow-up, indicating that fracture and surgery affected BIA measurements. Figure 3 and 4. The difference in resistance or reactance between fractured and non-fractured hip did not vary by type of surgical implant, either during hospital stay or at follow-up.

Discussion

Our results show that BIA is not affected by the type of surgical implants of the hip. There is a statistically and clinically relevant effect of fracture and/or surgery on resistance in the fractured hip, including important outliers. The clinical relevance is illustrated by the mean difference and limit of agreement of appendicular lean mass determined by BIA on the fractured and the unfractured side, using the equation of Sergi et al (17). In hospital the mean difference is 0.2 kg ($n=57$), with a large limit of agreement of -5.7 to 6.0 kg. At follow-up the limit of agreement is narrower, -3.0 to 2.6 kg, with a mean bias of -0.2 kg. A clinically relevant change in appendicular lean mass is of a magnitude of 1kg (7). A practical solution to this problem is to measure the unfractured side.

We performed the BIA measurements in a correct and competent manner, but we did not adhere to all recommendations for increasing precision of the BIA measurements. Some of these recommendations are controversial and the strict adherence to all such recommendations is impractical (18).

We found that resistance is affected by recent fracture or surgery. Our results do not inform us if it is the fracture, the surgery or a combination that influences BIA readings. A future study which examined BIA readings after fracture, but before surgery could possibly answer that question. We are not aware of previous studies on the effect of fracture and surgery on BIA measurements. A study by Villani et al used BIA in patients with acute hip fracture (19), but they performed all measurements on the right side, irrespective of the side of fracture. A study by Gonzalez-Montalvo et al used BIA after hip fracture and before surgery, but they only measured BIA on the contralateral side to the fracture (20).

Our results indicate that BIA is not affected by type of surgical implant of the three categories we examined. Hip arthroplasty, cannulated screws and compression hip screws have different masses and placement in the hip region. We believe that if the shape and the approximate shape of the different tissues of bone, fat and skeletal muscle mass are unchanged the type of surgical implant does not matter. It seems likely that more severe traumatic injuries where the shape of the hip is fundamentally changed or a tissue compartment is removed can result in larger changes in resistance or reactance.

It is possible that other acute changes could influence BIA readings in hospital. Patients could suffer from fluid and electrolyte disturbances due to illness, dehydration or fluid retention due to heart failure. We do not have information about these factors.

Even if the included population is not generalizable to all hip fracture patients, we believe the edema and tissue destruction associated with fracture and surgery is representative of all hip fracture patients. The surgical implants used in this study, predominantly compression hip screws, hip arthroplasty and cannulated screws, are the same as most patients with hip fracture are surgically treated.

This is the first time BIA is critically examined in a setting of acute tissue destruction and our findings indicate that care must be taken if BIA is to be used in similar settings, such as in other forms of surgery or trauma.

We note that the wide dispersion of results with outliers continue to be a problem for precise BIA measurements at an individual level.

Conclusion

Tetrapolar single frequency BIA is affected by recent surgery and fracture, but not by type of surgical implant. BIA can be used to determine body composition in patients who have suffered hip fracture. We recommend measuring the contralateral side to the hip fracture in the immediate postoperative period. This supports using BIA to determine body composition in patients with surgical implants.

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Conflicts of interest

The authors declare no conflict of interest.

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PAPER III

*Sarcopenia in patients with hip fracture:
A multicenter cross-sectional study.*

III

RESEARCH ARTICLE

Sarcopenia in patients with hip fracture: A multicenter cross-sectional study

Ole Martin Steihaug¹, Clara Gram Gjesdal^{2,3}, Bård Bogen^{1,4}, Målfrid Holen Kristoffersen⁵, Gunhild Lien⁶, Anette Høyen Ranhoff^{1,2*}

1 Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway, **2** Department of Clinical Science, University of Bergen, Bergen, Norway, **3** Department of Rheumatology, Haukeland University Hospital, Bergen, Norway, **4** Bergen University College, Bergen, Norway, **5** Department of Orthopedics, Haukeland University Hospital, Bergen, Norway, **6** Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

* ahranhoff@yahoo.no



Abstract

Background

Sarcopenia is prevalent in older persons and is a risk factor for falls, fractures, and mortality. The aim of this study was to determine a) the feasibility of determining sarcopenia in patients with acute hip fracture, b) the prevalence of sarcopenia and c) associations of sarcopenia with nutritional status and comorbidities.

Methods

A multicenter cross-sectional study on sarcopenia in male and female patients with acute hip fracture. Participants were previously ambulatory and living in the community. Sarcopenia was assessed postoperatively with muscle mass estimated by anthropometry using triiceps skinfold, arm circumference, height, weight and sex. Grip strength was measured by Jamar dynamometer and pre-fracture mobility was by self-report using the New Mobility Score.

Results

Out of 282 patients, 202 were assessed for sarcopenia of whom 74 (37%) were diagnosed as sarcopenic. Sarcopenia was associated with age, odds ratio (OR) 1.4 per 5 years, 95% confidence interval (CI) [1.1, 1.8], ASA Physical Status Classification System score, OR 2.3 per point, 95% CI [1.3, 4.3] and number of medications at discharge, OR 1.2 per medication, 95% CI [1.0, 1.3] and inversely associated with BMI, OR 0.8, 95% CI [0.7, 0.9] and serum albumin, OR 0.9, 95% CI [0.8, 1.0].

Conclusions

Thirty-seven percent of assessed subjects were diagnosed with sarcopenia. Our data demonstrates that the prevalence of sarcopenia is associated with older age, malnutrition and comorbidities. Determining sarcopenia at the bedside was feasible in postoperative hip

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Data Availability Statement: Due to ethical restrictions imposed by the Regional Committee for Medical and Health Research Ethics, REK sør-øst B, the data underlying this study are available upon request. The Regional Committees for Medical and Health Research Ethics are appointed by the Norwegian Ministry of Education and Research. Request for data access may be submitted to the medical director at Haraldsplass Deaconess Hospital, Petter Thornam: Email: petter.lave.thornam@haraldsplass.no. Website: <https://www.haraldsplass.no/>.

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fracture patients by using grip strength, estimation of muscle mass by anthropometry and self-reported mobility.

Introduction

Sarcopenia is a syndrome characterized by reduced muscle mass and reduced muscle function and an increased risk of disability and death [1]. Sarcopenia has recently been recognized as an independent condition with an International Classification of Disease Code [2]. Sarcopenia is a well-known risk factor for both falls and fractures: Reduced muscle strength makes it more difficult to regain lost balance and decreases the mechanical loading of the skeleton leading to reduced adaptive bone remodeling [3, 4]. Half of all hip fracture survivors will develop permanent impairments in mobility and 10–20% will become institutionalized [5]. The prevalence of sarcopenia in hip fracture patients is 17–74%, depending on population and definition of sarcopenia [6–8]. Norway has one of the highest rates of hip fracture in the world [9] and it is estimated that 4–5% of all deaths in the Norwegian population aged 50+ are attributable to hip fractures [10]. The reasons for this are unknown and sarcopenia is a candidate for explaining some of this excess risk. There has been only moderate improvement in the outcomes of patients with hip fracture since the 1960s [11]. Studies indicate that better outcomes are possible by involving geriatricians and increasing the intensity of rehabilitation efforts [12, 13]. Exercise and nutritional interventions are important interventions for sarcopenia [14] and in rehabilitation after hip fracture [15]. Smoking cessation and reduction of harmful alcohol intake can possibly reduce sarcopenia [16–18] and the risk of hip fracture [19–22]. There is no consensus on how sarcopenia should be operationalized. The three main methods are: low muscle mass as recommended by Janssen et al [23], low muscle mass with one of reduced physical performance or muscle strength, as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) [1] and low muscle mass and low grip strength, as recommended by the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project [24]. These recommendations are based on studies on older people living in the community. Investigating the feasibility of determining sarcopenia in acute hip fracture patients is necessary before assessment of sarcopenia can be introduced in clinical practice. The aims of this study are to:

1. assess the feasibility of determining sarcopenia in acute hip fracture patients.
2. determine the prevalence of sarcopenia and investigate how sarcopenia is associated with risk factors for adverse clinical outcomes: older age and male sex [10], nutritional risk and low albumin, low vitamin D, low body mass index (BMI) [25], comorbidities and polypharmacy, and impairments in activities of daily living [26].
3. Investigate the separate associations of muscle mass, grip strength and mobility with the same risk factors.

Materials and methods

This is a cross-sectional study on sarcopenia in patients with hip fracture. Patients were included in the immediate postoperative period at three hospitals in Norway, 2011–2013. Patients eligible for participation were 65 years or older, ambulatory before the hip fracture and willing to provide written informed consent. Permanent residents of nursing homes, patients who were medically unstable or had a life expectancy of less than 3 months, were

excluded. Collection of data was by the authors or research personnel, with different teams at the different hospitals. All personnel received training and guidance from the first author (OMS). Research staff were not present on the wards at all times, such as during weekends or holidays. Pre-fracture independence in activities of daily living (meals, bathing, grooming, dressing, continence, toileting, transferring and ambulation) was determined by the modified Barthel index (B-ADL), a summary score with a range 0–20 [27]. Nutritional risk was assessed using the Nutritional Risk Screening Score 2002 (NRS 2002) [28]. The NRS 2002 is a screening tool for identifying hospitalized patients likely to benefit from nutritional interventions. It is scored 0–3 points for nutritional state, 0–3 points for illness severity and an additional point if aged >70 years, for a total of score 0–7. Patients with hip fracture will typically be given one point for illness severity. Serum albumin and 25-OH vitamin D was measured in the fasting state, preoperatively at one hospital and postoperatively at two hospitals. Participants use of supplemental vitamin D (as tablets or cod liver oil) was determined by food frequency questionnaire and chart review. Comorbidities were assessed by chart review for determining the Charlson index [29]. The Charlson index is a list of chronic diseases, weighted by severity, that has been found to predict mortality. The American Society of Anesthesiologists Physical Status Classification System (ASA) score is a grading system of the preoperative health of surgical patients, range 1–5 [30]. The number of medications used regularly and as needed was assessed at discharge.

Determining sarcopenia

Participants were identified as being “not sarcopenic” or “sarcopenic” using the criteria recommended by the EWGSOP [1]. To be categorized as sarcopenic participants had to have low muscle mass and one of either low grip strength or low mobility. Total body muscle mass was estimated by anthropometry by the method of Heymsfield et al. [31] using gender, height, arm circumference and triceps skinfold. Arm circumference was measured on the right arm at the mid-point between the acromion and olecranon process with the arm hanging down. Triceps skinfold was measured on the posterior aspect of the same arm at the same level using a skinfold caliper (Harpenden, Baly International, Great Britain). Measurements were repeated until two readings were within 1mm. The values for total body muscle mass were converted to appendicular lean mass (ALM) using model 1 of Kim et al [32]. It has previously been reported, using data from this study, that anthropometry by the Heymsfield method was able to identify patients with low muscle mass, compared to Dual Energy X-ray absorptiometry (DXA) [33]. Patients were weighed in light clothing using the scales available on the hospital wards. Height was measured by wall-mounted stadiometer, except for a few cases where the patient was unable to stand. In those cases, height measured at other time-points, self-reported height or the distance from heel to crown while lying in bed was used. Cut-points for low muscle mass were chosen based on the recommendations of the EWGSOP [1], ALM divided by height squared, $\leq 7.25 \text{ kg m}^{-2}$ for men and $\leq 5.67 \text{ kg m}^{-2}$ for women.

Grip strength was measured three consecutive times in one hand and immediately afterward on the other hand with a Jamar Hydraulic Dynamometer (Sammons Preston, USA) while the patient was sitting in bed or on a chair, with the elbow flexed, the wrist in the neutral position, and with verbal encouragement. There was a brief interval between attempts while the dynamometer was repositioned. The single best value of all six measurements was used. Low grip strength was defined as $\leq 30\text{kg}$ for men and $\leq 20\text{kg}$ for women, as recommended by the EWGSOP[1]. Grip strength and muscle mass was determined at daytime in the mainly bed-bound participants without consideration of meals, recent physical activity, bladder voiding or hydration.

Mobility was determined by the New Mobility Score (NMS). The NMS assesses mobility in the two weeks prior to the fracture by interview. It ranges 0–9; a score of zero indicates that the person is not ambulatory and nine indicates an ability to walk without assistance while shopping. The NMS predicts physical performance and mortality after hip fracture [34–36]. Low mobility was defined as NMS <5, based on the cut-point recommended for predicting mortality after hip fracture [34]. Anthropometry for determining muscle mass was chosen because it is an established technique for determining body composition [37], is in common use [38], inexpensive and more easily performed on patients with pain on mobilization compared to DXA. Estimating muscle mass by anthropometry in patients with acute hip fracture requires some effort, mainly in determining height and weight. Grip strength is quickly measured, but requires an alert patient able to take instruction and with reasonable hand function. The NMS was chosen because it was assumed that some participants would be unable to perform tests of physical performance and because self-reported mobility has been found to have similar psychometric and predictive properties to objective tests [39]. Mobility by the NMS can be determined in a minute in a bed-bound patient, as long as the patient or proxy is able to answer questions about pre-fracture mobility.

Ethics

All participation was by written, informed consent. Patients were included in the postoperative phase as pain and anxiety is less after surgery. Participating hospitals, Haralds plass Deaconess Hospital, Haukeland University Hospital and Diakonhjemmet Hospital, and the Regional Committee on Medical and Health Research Ethics approved the study (2011/1322/REK sør-øst B). The study was conducted according to the principles of the Declaration of Helsinki [40].

Statistical analysis

Participants were described according to sarcopenia status with median and interquartile range (IQR) or mean and standard deviation (SD) and the differences between groups were analyzed with the Mann–Whitney–Wilcoxon test. The association between sarcopenia as dependent variable and the different risk factors as independent variables was analyzed in separate logistic regression analyses with odds ratios (OR) and 95% confidence intervals (95% CI). Separate analysis was also performed with low muscle mass, low grip strength and low mobility as dependent variables. Regression analyses were adjusted for age, sex and BMI and analysis of vitamin D was additionally adjusted for using supplemental vitamin D. Age, sex and BMI were included in the models because they are established associations of grip strength and muscle mass [41]. $P < 0.05$ was considered significant. Analysis was by Stata 14.0 (Stata Corp., USA)

Results

Of the included 282 patients with acute hip fracture, low muscle mass was found in 61% (118/194), low grip strength in 52% (116/222), and low mobility in 8% (20/244). Sarcopenia prevalence was 37% (74/202). Fig 1 illustrates which participants were assessed for mobility, grip strength and muscle mass. Participants with sarcopenia were older, had evidence of nutritional risk as indicated by lower BMI, lower albumin and higher scores on the NRS 2002. Participants with sarcopenia were also characterized by longer hospital stay, higher ASA score at operation, used a greater number of medications at discharge and had more impairments in activities of daily living before the hip fracture (Table 1). Participants with missing values for sarcopenia status had lower B-ADL scores compared to those who did not have missing values, and

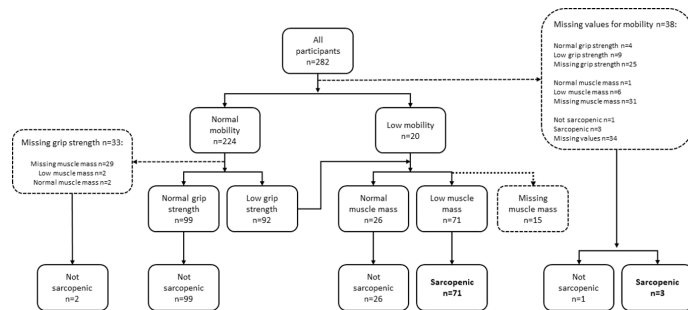


Fig 1. Participants assessed for mobility, grip strength and muscle mass.

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women with missing values had lower grip strength and mobility. Reasons for missing values included patients being too ill for or refusing specific examinations, or that they were discharged before the data collection was completed. Intra-articular fractures constituted 59% of the fractures. For 8% of patients this was their second hip fracture. Grip strength and ALM were determined at a median of 4 days after surgery, the interquartile range was 3 to 6 days, and the total range was from the day before surgery to 24 and 34 days after surgery, respectively. Supplemental vitamin D was used by 50% and was associated with a significantly higher serum vitamin D, 63 (SD 26) versus 47 (SD 23) $10^{-6} \text{ mol m}^{-3}$ (nmol/L). During the period of inclusion, 1592 patients were admitted for hip fracture surgery at the three hospitals.

The results of regression analysis for sarcopenia are presented in [Fig 2](#) and [Table 2](#). In adjusted analysis, sarcopenia was positively associated with age, OR 1.4 for each 5-year increase, 95% CI [1.1, 1.8], ASA score, OR 2.4, 95% CI [1.3, 4.3], and number of medications at discharge, OR 1.2, 95% CI [1.0, 1.3]. BMI, OR 0.8, 95% CI [0.7, 0.9] and serum albumin, OR 0.9 95% CI [0.8, 1.0], were associated with not having sarcopenia.

Results for the adjusted regression analyses for low muscle mass, low grip strength and low mobility are presented in [Table 3](#). Low muscle mass, using sex-specific cut-points, was associated with male gender, OR 5.4, 95% CI [1.8, 15.8]. BMI and albumin were negatively associated with low muscle mass. Low grip strength was associated with increasing age and ASA score and associated with lower BMI and albumin. Low mobility was associated with age and number of medications at discharge and negatively associated with impairments in activities of daily living.

Discussion

The aims of this study were to determine the feasibility of identifying sarcopenia in acute hip fracture patients, estimate the prevalence of sarcopenia and the associations between sarcopenia and risk factors for adverse clinical outcomes after hip fracture. Two hundred and eighty-two participants were included and sarcopenia status was determined in 202. Determining sarcopenia status using the bedside methods of anthropometry, grip strength and the NMS was feasible, is relevant to clinicians as a bedside tool, and is possible to implement on busy hospital wards. The rate of 28% of unsuccessful assessments for sarcopenia indicates that further improvement is warranted. Feasibility would be improved if muscle mass could be estimated without determining height or weight. Malmstrom and Morley have recommended the simple screening tool SARC-F as method to diagnose sarcopenia [42]. The SARC-F is a questionnaire containing 4 questions about physical performance and one question about falls in the last

Table 1. Characteristics of participants by sarcopenia status.

	Not sarcopenic, n = 128			Sarcopenic, n = 74		
	Median	IQR	n	Median	IQR	n
Age, years [IQR]	77.5	[70.5–85]	n = 128	82	[76–86]	n = 74**
Female, N (%)	99	(77)	n = 128	53	(72)	n = 74
Length of hospital stay, days [IQR]	6	[5–8]	n = 128	7.5	[6–11]	n = 74**
BMI, kg m ⁻² [IQR]	25.3	[22.7–28.0]	n = 110	22.0	[19.5–24.2]	n = 67**
NRS 2002 [IQR]	2	[2–2]	n = 117	2	[2–3]	n = 70**
Albumin, kg m ³ (SD)	35.9	(5.2)	n = 113	32.6	(6.3)	n = 59**
User of vitamin D supplement, N (%)	60	(50)	n = 119	31	(46)	n = 56
Vitamin D, 10 ⁻⁶ mol m ⁻³ [IQR]	53	[34–75]	n = 111	48	[31–66]	n = 64
Charlson index [IQR]	0.5	[0–1]	n = 128	1	[0–2]	n = 74
ASA score [IQR]	2	[2–3]	n = 128	3	[2–3]	n = 74**
Medications, number [IQR]	7	[5–10]	n = 128	8	[7–11]	n = 73**
B-ADL [IQR]	20	[19–20]	n = 88	20	[18–20]	n = 57*
ALM height ² , kg·m ⁻² [IQR]	6.4	[5.6–7.4]	n = 115	4.7	[4.0–5.2]	n = 74**
ALM height ² – Women, kg·m ⁻² [IQR]	6.3	[5.6–7.1]	n = 90	4.4	[4.0–5.1]	n = 53**
ALM height ² – Men, kg·m ⁻² [IQR]	7.1	[6.1–7.8]	n = 25	5.1	[4.5–5.8]	n = 21**
Grip strength, kg [IQR]	25	[21–32]	n = 126	17	[12–20]	n = 74**
Grip strength – Women, kg [IQR]	22	[20–26]	n = 96	14	[12–18]	n = 53**
Grip strength – Men, kg [IQR]	40	[34–43]	n = 29	24	[20–27]	n = 22**
New Mobility Score [IQR]	9	[7–9]	n = 127	7	[5–9]	n = 71**
New mobility score–Women [IQR]	9	[7–9]	n = 98	7.5	[5–9]	n = 52**
New mobility score–Men [IQR]	9	[7–9]	n = 29	7	[5–9]	n = 19*

IQR: Values are medians and interquartile range. SD: Values are means and standard deviation.

* P ≤ 0.05 or

**P ≤ 0.01 is the probability for difference by Mann–Whitney–Wilcoxon test.

BMI: Body mass index. ASA score: The ASA Physical Status Classification System. Barthel ADL: Barthel activities of daily living. ALM: Appendicular lean mass.

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year. Future research should investigate the role of the SARC-F in patients with hip fracture. In the present study, sarcopenia was determined by anthropometry, which is considered a less precise method compared to DXA or bioelectrical impedance analysis. Anthropometry is adequate at identifying low muscle mass [43] and is able to identify increased mortality risk in males [44, 45]. Because of pain and severe mobility impairment, it is difficult to measure muscle mass by DXA in patients with hip fracture. Compared to anthropometry, DXA is more expensive, requires bulky equipment, takes longer time to do, and requires more trained personnel. DXA estimates of muscle mass are sensitive to acute changes in muscle water content, such as seen with changes in muscle glycogen or creatinine due to feeding or dehydration [46].

A strength of the present study is that participants were recruited at three separate hospitals. This reduced the influence of investigator specific factors such as confirmation bias and reduced the influence of hospital related factors such as differences in quality of care, differences in catchment populations, or selective recruitment processes. A multi-center study is leads to greater generalizability of results. A weakness of the multi-center design was less control of the conduct of the study, leading to loss of information on participants who were screened but not included and missing values.

Three recent cross-sectional studies have investigated sarcopenia in acute hip fracture patients using the EWGSOP framework. There was great variation in the prevalence of

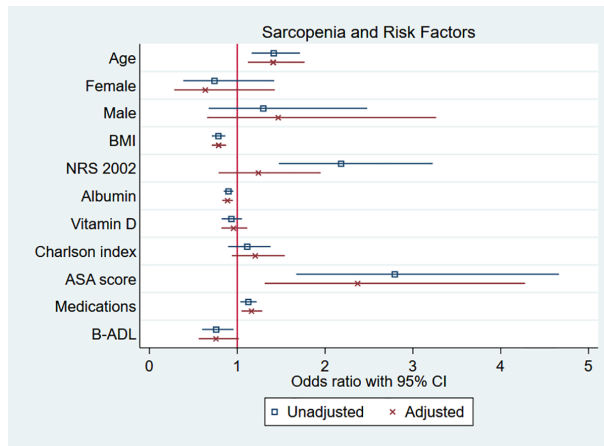


Fig 2. Sarcopenia and risk factors. Adjusted regression analysis using age, sex and BMI as covariates and the analysis of vitamin D additionally adjusted for being a user of supplemental vitamin D. Estimate for age is for 5-year increase and estimate for vitamin D is for increase of 10^{-5} mol m⁻³ (10 nanomol/L).

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sarcopenia, 12–74% in men and 18–68% in women [6–8]. This variation in the prevalence of sarcopenia is likely due to differences in patient groups, measurement techniques and the use of different cut-points. The studies were from Hong Kong, Spain and Italy. Ho et al studied Chinese patients with hip fracture and used lower cut-points for grip strength at <26kg for men and <18kg for women. Muscle mass was determined by DXA a mean 14 days after the fracture. In the study by Gonzalez-Montalvo et al sarcopenia was determined before surgery. Muscle mass was determined by bioelectrical impedance and the cut-point for low muscle mass was higher than in the present study, at <6.68 kg·m⁻² in women and <8.31 kg·m⁻² in

Table 2. Predictors of sarcopenia.

	Univariable analysis					Adjusted analysis				
	OR	[95% CI]	P-value	R ²	n	OR	[95% CI]	P-value	R ²	n
Age, 5 years	1.4	[1.2, 1.7]	<0.001	0.05	202	1.4	[1.1, 1.8]	0.003	0.18	177
Female	0.7	[0.4, 1.4]	0.4	<0.01	202	0.6	[0.3, 1.4]	0.3	0.18	177
Male	1.4	[0.7, 2.6]	0.3	<0.01	202	1.6	[0.7, 3.5]	0.3	0.18	177
BMI, kg m ⁻²	0.8	[0.7, 0.9]	<0.001	0.13	177	0.8	[0.7, 0.9]	<0.001	0.18	177
NRS 2002	2.2	[1.5, 3.2]	<0.001	0.08	187	1.2	[0.8, 1.9]	0.4	0.19	168
Albumin, kg m ⁻³	0.9	[0.8, 1.0]	<0.001	0.06	172	0.9	[0.8, 1.0]	0.001	0.19	147
Vitamin D, 10 ⁻⁵ mol m ⁻³	0.9	[0.8, 1.1]	0.3	<0.01	175	1.0	[0.8, 1.1]	0.6	0.17	141
Charlson index	1.1	[0.9, 1.4]	0.3	<0.01	202	1.2	[0.9, 1.5]	0.1	0.18	177
ASA score	2.8	[1.7, 4.7]	<0.001	0.06	202	2.4	[1.3, 4.3]	0.004	0.21	177
Medications	1.1	[1.0, 1.2]	0.005	0.03	201	1.2	[1.0, 1.3]	0.004	0.22	176
B-ADL	0.8	[0.6, 1.0]	0.020	0.03	145	0.8	[0.6, 1.0]	0.066	0.25	139

Sarcopenia as dependent variable in separate logistic regression analyses. Adjusted analyses are with age, gender and BMI as covariates and for vitamin D as a predictor is additionally adjusted for being a user of supplemental vitamin D. OR: Odds ratio. CI: Confidence interval. R²: Adjusted R². BMI: Body mass index. ASA score: the ASA Physical Status Classification System, points. B-ADL: Barthel activities of daily living. Vitamin D 10⁻⁵ mol m⁻³ (10 nmol/L).

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Table 3. Muscle mass, grip strength, mobility and risk factors.

	Low muscle mass					Low grip strength					Low mobility				
	OR	[95% CI]	n	P	R ²	OR	[95% CI]	n	P	R ²	OR	[95% CI]	n	P	R ²
Age, 5 years	1.0	[0.8, 1.3]	170	0.97	0.27	1.6	[1.3, 2.0]	186	<0.001	0.15	1.5	[1.0, 2.2]	194	0.038	0.07
Female	0.2	[0.1, 0.6]	170	0.002	0.27	1.2	[0.6, 2.6]	186	0.6	0.15	0.6	[0.2, 2.2]	194	0.5	0.07
Male	5.4	[1.8, 15.8]	170	0.002	0.27	0.8	[0.4, 1.7]	186	0.6	0.15	1.6	[0.4, 5.5]	194	0.5	0.07
BMI, kg m⁻²	0.7	[[0.6, 0.8]	170	<0.001	0.27	0.9	[0.8, 1.0]	186	0.003	0.15	0.9	[0.8, 1.0]	194	0.2	0.07
NRS 2002	1.6	[0.8, 3.3]	163	0.2	0.27	1.1	[0.8, 1.7]	175	0.6	0.17	1.5	[0.9, 2.6]	182	0.1	0.10
Albumin, kg m⁻³	0.9	[0.8, 0.9]	141	0.001	0.31	0.9	[0.9, 1.0]	154	0.006	0.17	1.0	[0.9, 1.1]	163	0.9	0.03
Vitamin D, 10⁻⁵ mol m⁻³	1.0	[0.8, 1.1]	138	0.6	0.31	0.9	[0.7, 1.0]	147	0.059	0.17	0.9	[0.6, 1.2]	154	0.4	0.10
Charlson index	1.1	[0.8, 1.4]	170	0.7	0.27	1.1	[0.9, 1.4]	186	0.4	0.15	1.3	[0.9, 1.8]	194	0.2	0.09
ASA score	1.9	[1.0, 3.6]	170	0.052	0.29	1.8	[1.0, 3.0]	186	0.038	0.16	2.3	[0.9, 6.2]	194	0.09	0.10
Medications	1.0	[0.9, 1.2]	169	0.5	0.28	1.1	[1.0, 1.2]	185	0.08	0.16	1.2	[1.0, 1.5]	193	0.015	0.13
B-ADL	0.9	[0.6, 1.3]	131	0.5	0.31	0.8	[0.6, 1.0]	148	0.052	0.19	0.5	[0.3, 0.7]	149	<0.001	0.34

Low muscle mass, low grip strength and low mobility as dependent variables in separate logistic regression analyses. All analyses are adjusted for age, gender and BMI and analyses for serum vitamin D are additionally adjusted for use of supplemental vitamin D. OR: Odds ratio. CI: Confidence interval. n: number of participants without missing values and available for analysis. P: Probability of association being random. R²: Adjusted R². BMI: Body mass index. ASA score: the ASA Physical Status Classification System, points. B-ADL: Barthel activities of daily living. ALM: Appendicular lean mass. Low muscle mass ≤ 7.25 kg m⁻² for men and ≤ 5.67 kg m⁻² for women, defined as appendicular lean mass divided by height squared. Low grip strength is ≤ 30 kg for men and ≤ 20 kg for women. Low mobility is NMS < 5 . Vitamin D 10^{-5} mol m⁻³ (10 nmol/L).

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men. The study by Di Monaco et al was on Italian women selected to undergo intensive rehabilitation after hip fracture. Di Monaco et al found that the Barthel index at the start of rehabilitation was lower in the group with sarcopenia, while both the study by Gonzalez-Montalvo et al. and Di Monaco et al. reported an association between low BMI and sarcopenia [6, 8].

Compared to the patients in the Norwegian Hip Fracture Register, which covers 86–94% of all hip fractures in Norway, the patients in our study had a mean age of 79.4 years and a mean ASA score of 2.5, compared to 80.0 years, and an ASA score of 2.7 in the register [47]. Our results are not generalizable for hip fracture patients from nursing homes, or patients with severe physical or cognitive impairment. However, the relatively robust participants in our study are more likely to benefit from intensive rehabilitation compared to frailer patients, as found by a study by Prestmo et al on the benefit of orthogeriatric care in frail versus fit hip fracture patients [48].

Increasing age was associated with sarcopenia and low grip strength, but not with low muscle mass, which is in agreement with previous research on healthy older people [49]. There is a significant association between low BMI and sarcopenia in other studies on sarcopenia in hip fracture patients [6, 8], which is consistent with the finding that BMI is negatively associated with sarcopenia, muscle mass and grip strength. Nutritional risk by NRS 2002 was associated with sarcopenia in unadjusted analysis, but not in adjusted analysis. This is explained by how NRS 2002 is scored, with higher scores for low BMI and age greater than 70 years. The NRS 2002 was developed as screening tool for identifying hospitalized patients likely to benefit from nutritional interventions, and is not primarily a tool to diagnose undernutrition. Albumin is a biomarker of undernutrition and is a risk factor for mortality in hip fracture patients [50]. In the present study, low albumin was associated with sarcopenia, low muscle mass and low grip strength. Serum albumin and vitamin D are reduced in inflammatory states [51] such as in hip fracture or surgery, and thus caution is warranted when interpreting this association. There are numerous studies describing important associations between serum albumin and

clinical outcomes in patients with hip fracture, where serum albumin has been measured both before [52], and after surgery [53]. Visser et al [54] found an increased loss of muscle mass in participants with low serum albumin in older persons living in the community, which indicates a relevant association between sarcopenia and albumin in a setting without acute inflammation. The finding in this study that low BMI and serum albumin are associated with sarcopenia supports the hypothesis that nutrition and sarcopenia are associated and that nutritional interventions such as supplemental protein, specific amino acids or β -hydroxy- β -methylbutyrate can improve muscle mass, strength and physical performance [55–58]. The present study found no association between serum vitamin D and sarcopenia, which is in agreement with the study by Gonzalez-Montalvo et al [6] on sarcopenia in hip fracture patients. Participants in this study had higher levels of serum vitamin D compared to other studies on patients with hip fracture [59, 60], likely explained by the fact that half the participants used supplemental vitamin D before the fracture. The ASA score and the number of chronic diseases are predictors of mortality after hip fracture [26]. Polypharmacy or use of potentially inappropriate medication has been found to increase the risk of hip fracture [61], the risk of injurious falls after hip fracture [25], and reduced mobility and grip strength in hospitalized elderly [62]. In the present study, there was an association between higher ASA score, using more medications and sarcopenia, but no association between the Charlson index and sarcopenia. There is probably a causal relationship between comorbidities, polypharmacy and sarcopenia. Future studies should examine the effect on sarcopenia by reducing inappropriate polypharmacy [63]. The participants in the present study had low values on the Charlson index with a median score of one. Many common chronic conditions, such as hypertension, angina or osteoporosis are not counted as part of the Charlson index and it is possible that the index does not fully capture the burden of chronic diseases.

The associations found in the present study between sex and low muscle mass, low grip strength and reduced mobility, had wide confidence intervals. This indicates that the methods for determining muscle mass, grip strength and mobility and risk factors were insufficiently precise or that there were too few male participants with data on sarcopenia status in the study, only 50 out of 202. Men have a worse prognosis after hip fracture with a 4.6-fold increased mortality after hip fracture compared to 2.8-fold increase in women [10]. The reasons for this are unclear and at odds with other research that has found a greater prevalence of physical frailty in women [64]. Di Monaco et al [65] found that male patients with hip fracture were more likely to have low muscle mass using sex specific cut-points, and our results agree with this. Future studies should examine if low muscle mass in men with hip fracture can explain the excess mortality.

Conclusion

Among previously ambulatory, community-living hip fracture patients, the prevalence of sarcopenia was 37%. Sarcopenia was positively associated with age, ASA score and polypharmacy, and negatively associated with BMI and albumin. By using anthropometry, grip strength and self-reported mobility it is feasible to determine sarcopenia at the bedside in postoperative hip fracture patients.

Author Contributions

Conceptualization: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Gunhild Lien, Anette Hølen Ranhoff.

Data curation: Ole Martin Steihaug, Gunhild Lien.

Formal analysis: Ole Martin Steihaug.

Funding acquisition: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Anette Hysten Ranhoff.

Investigation: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Målfrid Holen Kristoffersen, Gunhild Lien, Anette Hysten Ranhoff.

Methodology: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Målfrid Holen Kristoffersen, Gunhild Lien, Anette Hysten Ranhoff.

Project administration: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Anette Hysten Ranhoff.

Resources: Clara Gram Gjesdal, Bård Bogen, Målfrid Holen Kristoffersen, Gunhild Lien, Anette Hysten Ranhoff.

Supervision: Clara Gram Gjesdal, Bård Bogen, Målfrid Holen Kristoffersen, Gunhild Lien, Anette Hysten Ranhoff.

Validation: Ole Martin Steihaug.

Visualization: Ole Martin Steihaug, Bård Bogen.

Writing – original draft: Ole Martin Steihaug.

Writing – review & editing: Ole Martin Steihaug, Clara Gram Gjesdal, Bård Bogen, Målfrid Holen Kristoffersen, Gunhild Lien, Anette Hysten Ranhoff.

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PAPER IV

*Does sarcopenia predict change in mobility
after hip fracture? a multicenter observational
study with one-year follow-up.*

IV

RESEARCH ARTICLE

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Does sarcopenia predict change in mobility after hip fracture? a multicenter observational study with one-year follow-up

Ole Martin Steihaug¹, Clara Gram Gjesdal^{2,3}, Bård Bogen^{1,4}, Målfrid Holen Kristoffersen⁵, Gunhild Lien⁶, Karl Ove Hufthammer⁷ and Anette Hylen Ranhoff^{1,2,8*}

Abstract

Background: Patients with hip fracture frequently have sarcopenia and are at great risk of loss of mobility. We have investigated if sarcopenia predicts change in mobility after hip fracture.

Methods: This is a prospective, multicenter observational study with one-year follow-up. Patients with hip fracture who were community-living and capable of walking before the fracture were included at three hospitals in Norway (2011–2013). The primary outcome of the study was change in mobility, measured by the New Mobility Score (NMS). Sarcopenia was determined postoperatively by anthropometry, grip strength, and NMS.

Results: We included 282 participants and sarcopenia status was determined in 201, of whom 38% (77/201) had sarcopenia, 66% (128/194) had low muscle mass, 52% (116/222) had low grip strength and 8% (20/244) had low pre-fracture mobility (NMS < 5). Sarcopenia did not predict change in mobility (effect 0.2 points; 95% CI –0.5 to 0.9, $P = 0.6$), but it was associated with having lower mobility at one-year (NMS 5.8 (SD 2.3) vs. 6.8 (SD 2.2), $P = 0.003$), becoming a resident of a nursing home (odds ratio 3.2, 95% CI 0.9 to 12.4, $P = 0.048$), and the combined endpoint of becoming a resident of a skilled nursing home or death (odds ratio 3.6, 95% CI 1.2 to 12.2, $P = 0.02$).

Conclusions: Sarcopenia did not predict change in mobility in the year after hip fracture.

Keywords: Activities of daily living, Hip fractures, Independent living, Mobility limitation, Skilled nursing facilities, Sarcopenia

Background

A hip fracture is associated with severe and persisting mobility impairment in more than half of patients [1]. For the last 30 years, a substantial effort has been made to understand the condition of sarcopenia, and several definitions have been proposed [2]. Sarcopenia has recently been recognized as an independent condition with its own ICD-10 code [3]. One of the most widely used definitions is by the European Working Group on Sarcopenia in Older Persons (EWGSOP): low muscle mass with low muscle strength or

low physical performance [4]. Previous studies on sarcopenia in patients with hip fracture have been cross-sectional, single-center, have included few participants or have had short follow-ups [5–10]. The three components of EWGSOP sarcopenia have different associations with mobility after hip fracture. Physical performance and mobility are strong determinants of mobility after hip fracture [11, 12]. Muscle strength is a somewhat weaker predictor [13, 14], whereas the studies on muscle mass have been inconclusive [15]. Our primary hypothesis is that sarcopenia, determined by methods suitable for bed-side use, predicts change in mobility in the year after hip fracture and therefore that sarcopenia status is useful for determining prognosis and is a possible cause of mobility impairment. Further, we aim to describe the associations of sarcopenia and the individual

* Correspondence: ahrhanhoff@yahoo.no

¹Kavli Research Centre for Geriatrics and Dementia, Haralds plass Deaconess Hospital, Bergen, Norway

²Department of Clinical Science, University of Bergen, Bergen, Norway

Full list of author information is available at the end of the article



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components of sarcopenia (muscle mass, grip strength and mobility) and adverse clinical outcomes in the year after hip fracture: change in activities of daily living, reoperations for hip fracture, all-cause hospitalization, fractures, becoming a resident of a nursing home or death.

Methods

Study design

We conducted a prospective observational study of sarcopenia in patients with acute hip fracture with follow-up at three months and one year, conducted at three Norwegian hospitals in 2011–2013.

Participants

Participants were included while in hospital in the postoperative phase. Eligible participants were aged ≥ 65 years, able to give informed consent as judged by experienced clinicians, were living in the community, and were ambulatory before the fracture. Patients who were unstable such as with delirium, acute respiratory failure or in severe pain were not eligible. Other exclusion criteria were dementia when it made informed consent impossible, remaining life expectancy of less than three months and bone disease other than osteoporosis or osteomalacia. We screened for participants by examining lists of patients admitted for hip fracture or staying on the hospital wards.

Data collection

Information was collected by the authors and study personnel by examination, chart review, routine blood tests and by interviews with patients and their caregivers from the first postoperative day and until discharge from hospital. Weight was measured with the scales on the hospital wards. We collected the American Society of Anesthesiologists (ASA) score, Charlson comorbidity index [16], Barthel activities of daily living (B-ADL) score [17], length of the acute care hospital stay, previous hip fracture and type of hip fracture. Follow-up was at 3 months at an outpatient clinic and at one year as a telephone interview with the patient or care-giver. Information on previous and subsequent hip fractures, and reoperations for the index hip fracture came from the Norwegian Hip Fracture Register [18]. This register started data collection in 2005 and has coverage on an estimated 90% of all hip fractures in Norway. The register has information on reoperations, with an estimated coverage of 65% of hip fractures treated with surgical pinning, 68% after hemiarthroplasty and 93% after total hip replacement [19]. Mortality data was supplied by the National Population Register, which is complete.

Sarcopenia

Participants were classified as sarcopenic if they had low muscle mass and either low grip strength or impaired

mobility, as described by the EWGSOP [4]. Total body muscle mass was determined by anthropometry by the method of Heymsfield et al. using height, arm circumference and triceps skinfold [20]. Arm circumference was measured on the right arm using a non-elastic tape at the mid-point of the acromion and olecranon process, and triceps skinfold was measured on the posterior aspect of the same arm at the same level using a skinfold caliper (Harpندن, Baly International, Great Britain). Height was measured by a wall mounted stadiometer, or if the patients was unable to stand self-reported height was used. If the participant was unable to stand or report their height, the length from heel to crown was measured while lying in bed. In cases with missing value on height at baseline, height measured at follow-up was used. The values for total body muscle mass were transformed to appendicular lean mass (ALM) using model 1 described by Kim et al. [21]. The cut-points for low muscle mass were $ALM \leq 7.25 \text{ kg/m}^2$ for men and $\leq 5.67 \text{ kg/m}^2$ for women. We chose anthropometry for its ease of use at the bed-side in immobile hip fracture patients. Grip strength was measured with a Jamar Hydraulic Dynamometer (Sammons Preston, USA) while the patient was sitting in bed or on a chair with the elbow flexed, the wrist in the neutral position and with verbal encouragement. Grip strength was measured three times on each hand with short intervals between each attempt while the grip was repositioned. The single best value out of these six measurements was used. Low grip strength was $\leq 30 \text{ kg}$ for men and $\leq 20 \text{ kg}$ for women. Mobility in the two weeks before the hip fracture was determined by interview using the New Mobility Score (NMS). The NMS is scored 0–9 according to a person's ability to walk indoors, outdoors, or while shopping [22]. The cut-point for low mobility was chosen as < 5 , as this has been used to predict mortality after hip fracture [23]. We used a Danish version of the NMS with minimal modifications to Norwegian. Sarcopenia status was determined postoperatively and at follow-up.

Outcome measures

The primary outcome was change in mobility, calculated as NMS at one year minus the pre-fracture NMS. We believe that change in mobility is more relevant than mobility for identifying patients who are more likely to benefit from interventions. We determined mobility pre-fracture, at three months, and at one-year. All other analyses were considered exploratory. Other outcome variables at one year were NMS at one year, B-ADL at one year, change in B-ADL, new clinical fractures, new hip fractures, reoperation for hip fracture, all-cause hospitalizations, death, becoming a permanent resident of a skilled nursing home, and the combined endpoint of becoming a permanent resident of a nursing home or

death. The combined endpoint was chosen because death and becoming a resident of a nursing home are competing risks. New clinical fracture was any symptomatic skeletal fracture reported by the patient.

Statistical analysis

We report descriptive data as means with standard deviations or as counts with percentages. To examine the predictive effect of sarcopenia status on changes in mobility and level of activity of daily living, we used linear regression analyses with NMS and B-ADL as response variables and sarcopenia status at baseline (sarcopenic vs. not sarcopenic) and age, sex and BMI as predictors. Age, sex and BMI were included in the models because they are established predictors of mobility after hip fracture [24] or sarcopenia [25]. The relationship with age and BMI was not assumed to be linear and was modelled using restricted cubic splines with 3 knots, placed at the 10%, 50% and 90% quantiles. We assumed that a one-point change in NMS would be clinically significant. We used Fisher's exact test for the analysis of sarcopenia associated with new clinical fracture, new hip fracture, reoperations, all-cause hospitalization, becoming a resident of skilled nursing home, and the combined endpoint of nursing home or death. The association between the separate components of sarcopenia (muscle mass, grip strength and mobility) with change in mobility, change in B-ADL and the combined endpoint of becoming a resident of a skilled nursing home or death was analysed using regression analysis. Muscle mass, grip strength and mobility were independent continuous variables, and were analyzed separately. Change in mobility and change in B-ADL were continuous, dependent variables and the combined endpoint of becoming resident of a nursing home or death was a dichotomous dependent variable.

For the regression analyses, we used multiple imputation (500 imputations), based on predictive mean matching, using the 'aregImpute()' function in the 'rms' R package [26]. The variables used in the imputation models were the ones included in the regression models, variables highly correlated with these variables and variables expected to explain the missing data mechanism: NMS at baseline, follow-up, and at one year, and change in NMS from baseline to one year, B-ADL before the hip fracture and change in B-ADL from pre-fracture until one year, sarcopenia status at baseline, BMI at baseline, ASA score during hip fracture surgery, previous hip fracture, serum albumin when in hospital, grip strength at follow-up, sex, clinical fractures and hip fractures in the year after admission, becoming a resident of a skilled nursing home, or dying in the following year. All continuous predictors were modelled linearly in the imputation model. The imputation analyses were done in R 3.3.0 [27] and the rest of the analyses were done in Stata 14 (Stata Corp., USA). *P*-values ≤ 0.05 were considered significant.

Results

All patients in hospital with confirmed hip fracture were considered for inclusion if the research staffs at the different hospitals were present. Some patients were unable to participate because they were discharged before the two-day consent process was completed. There was no systematic recording of the patients who were screened, but not included. Figure 1 describes the progress of participants through hip fracture, inclusion in the study and follow-up. During the period of inclusion 1592 patients had surgery for hip fracture and 282 patients were included in the study.

Mean age was 79.4 (SD 8.2) years and 76% were female. Mean BMI was 24.1 (SD 4.3) kg/m², with a wide range 13.0 to 44.7 kg/m². See Table 1 for baseline demographics. One patient died during the hospital stay. Participants who had missing data on sarcopenia status during hospitalization had lower pre-fracture NMS and pre-fracture B-ADL and were more likely to become a permanent resident of a skilled nursing home. For 69 participants, height was not assessed during the hospital stay, and for 52 of these, height determined at follow-up was used.

Sarcopenia

Sarcopenia status during hospitalization for hip fracture was determined in 201 participants, and 39% (77/201) had sarcopenia. Low muscle mass was present in 66% (128/194) of the participants, low grip strength in 52% (116/222), and 8% had low pre-fracture mobility (19/243). One participant did not have muscle mass determined but had grip strength and NMS above the cut-points and was considered not-sarcopenic. Figure 2. Participants with sarcopenia were older, had lower BMI, greater ASA score at operation, greater prevalence of previous hip fracture and pulmonary disease and lower B-ADL before the fracture. Grip strength and ALM were assessed at a median of 4 days after surgery (interquartile range 3 to 6 days) (Fig. 2).

Outcomes after one year

Sarcopenia was not associated with change in mobility at one year in unadjusted or adjusted analyses (e.g., the change in NMS was an additional 0.2 in sarcopenic patients compared to non-sarcopenic patients, 95% CI: -0.5 to 0.9, *P* = 0.6); see Table 2 for outcomes at one-year. Sarcopenia status at hospitalization did not predict change in mobility from pre-fracture to 3 months, or from 3 months to one-year. Results were not affected by imputation of missing values. Mobility was reduced in 54% of participants one year after hip fracture, with a mean NMS of 6.4 (SD 2.2). See Fig. 3 for NMS by sarcopenia status during the year after hip fracture. Figure 4 describes the relationship between specific scores on the NMS pre-fracture and at one-year. Participants with sarcopenia had lower mobility at one-year, NMS 5.8 (SD

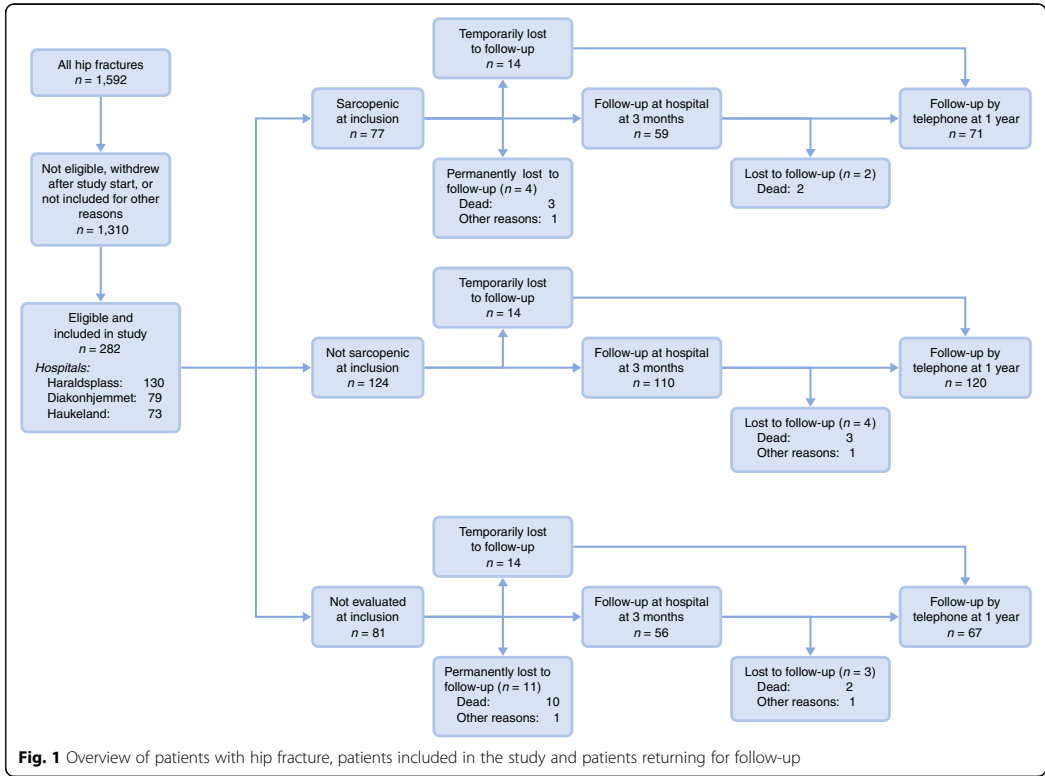


Fig. 1 Overview of patients with hip fracture, patients included in the study and patients returning for follow-up

2.3) vs. 6.8 (SD 2.2), $P = 0.003$, and greater impairment in B-ADL, 16.8 (SD 4.4) vs. 18.6 (SD 2.8), $P = 0.001$, compared to patients without sarcopenia. Sarcopenia was associated with becoming a permanent resident of a skilled nursing home (OR 3.2, 95% CI: 0.9 to 12.4, $P = 0.048$) and the combined endpoint of becoming a resident of a skilled nursing home or death (OR 3.6, 95% CI: 1.2 to 12.3, $P = 0.02$).

Muscle mass, grip strength and mobility

Muscle mass or grip strength was not associated with any outcome in adjusted analysis Table 3. In unadjusted analysis, grip strength and NMS were associated with a reduced risk of becoming a resident of a nursing home or death. The NMS was positively associated with change in B-ADL in adjusted analysis (estimate 0.2 per point, 95% CI 0.0 to 0.4, $P = 0.03$).

Discussion

The aim of this study was to investigate if sarcopenia predicted change in mobility after hip fracture. We found that sarcopenia status did not predict change in mobility in unadjusted analysis, which indicates that

sarcopenia is not useful in determining prognosis. Further, sarcopenia did not predict change in mobility in analysis adjusted for age, sex and BMI, which indicates that sarcopenia status is not likely to be causally related to developing reduced mobility. We used multiple imputation to reduce the loss of information associated with missing values. This approach is considered inferior to having all the data, but preferable to performing analysis on complete data. One assumption of multiple imputation is that missing values can be estimated by the remaining information in the dataset. The results of our analysis were similar when analyzing complete cases and when analyzing datasets with imputed values, indicating that the results of our analysis are valid even if this assumption was erroneous.

Change in mobility was not associated with sarcopenia and this was consistent across all the investigated time periods, from baseline to three months, from baseline to one year and from three months to one year. Mobility from before the hip fracture until one year is characterized by an initial loss of mobility and a subsequent partial recovery. Sarcopenia is not associated with either the loss of mobility or the recovery, which further supports

Table 1 Baseline characteristics of participants by sarcopenia status

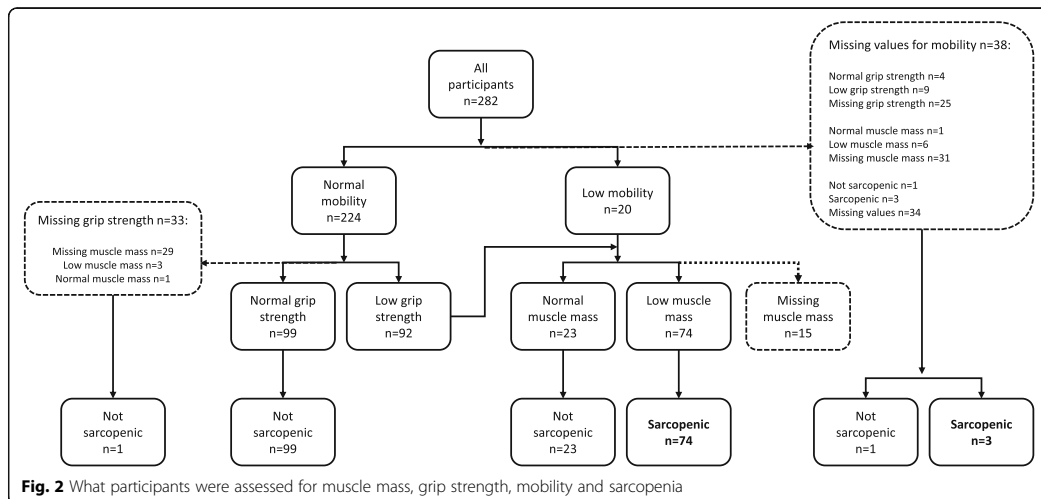
	Not sarcopenic		Sarcopenic		P-value
Age, years (SD)	77.1 (7.8)	n = 124	81.8 (7.6)	n = 77	< 0.0001
Female, n (%)	95 (77)	n = 124	56 (72)	n = 77	0.5
Barthel ADL pre-fracture (SD)	19.5 (1.1)	n = 85	18.7 (1.9)	n = 60	0.006
Type of hip fracture					0.6
Neck of femur, not displaced, n (%)	29 (24)	n = 123	14 (18)	n = 77	
Neck of femur, displaced, n (%)	46 (37)	n = 123	31 (40)	n = 77	
Trochanteric, n (%)	48 (39)	n = 123	32 (42)	n = 77	
ASA score (SD)	2.3 (0.6)	n = 124	2.7 (0.6)	n = 77	< 0.001
Previous hip fracture, n (%)	5 (4)	n = 124	9 (12)	n = 77	0.039
Charlson score (SD)	0.9 (1.3)	n = 124	1.1 (1.3)	n = 77	0.15
Heart failure, n (%)	7 (6)	n = 124	6 (8)	n = 77	0.5
Previous myocardial infarction, n (%)	14 (11)	n = 124	9 (12)	n = 77	0.9
Cerebrovascular disease, n (%)	13 (10)	n = 124	8 (10)	n = 77	0.98
Diabetes mellitus, n (%)	9 (7)	n = 124	10 (13)	n = 77	0.2
Any solid tumor, n (%)	7 (6)	n = 124	8 (10)	n = 77	0.2
Pulmonary disease, n (%)	15 (12)	n = 124	18 (23)	n = 77	0.036
Length of hospital stay, days (SD)	6.8 (2.7)	n = 124	9.6 (6.7)	n = 77	< 0.001
Body composition					
BMI, kg/m ² (SD)	25.6 (4.2)	n = 107	22.1 (3.7)	n = 70	< 0.001
ALM/height ² , kg/m ² (SD)	6.3 (1.5)	n = 111	4.4 (1.0)	n = 77	< 0.001
Women	6.1 (1.3)	n = 86	4.3 (0.8)	n = 56	< 0.001
Men	7.0 (1.7)	n = 25	4.8 (1.2)	n = 21	< 0.001
Grip strength					
Grip strength, kg (SD)	27.0 (10.3)	n = 123	16.5 (6.4)	n = 77	< 0.001
Women	22.9 (6.9)	n = 94	14.3 (5.0)	n = 56	< 0.001
Men	40.1 (8.3)	n = 29	22.3 (5.9)	n = 21	< 0.001
Mobility					
New Mobility Score (SD)	8.0 (1.5)	n = 123	7.1 (2.0)	n = 74	< 0.001
Women	8.0 (1.6)	n = 94	7.1 (2.0)	n = 55	0.008
Men	8.2 (1.4)	n = 29	6.8 (2.2)	n = 19	0.017

Baseline characteristics by sarcopenia status (means with standard deviations and counts with percentages). P-values for comparison of groups are by the Mann-Whitney-Wilcoxon test, except for type of fracture which is by chi-squared test. Trochanteric fractures include basocervical femoral neck fractures and subtrochanteric fractures. Previous hip fracture indicates a previous hip fracture, either left or right hip. ALM: Appendicular lean mass, ADL: Activities of daily living

that sarcopenia is not related to change in mobility. In contrast to change in mobility, being sarcopenic was associated with having lower mobility pre-fracture, at three months and at one year, compared to not being sarcopenic. This is expected, since low mobility is one criteria for sarcopenia. As seen in Fig. 4, pre-fracture mobility is a determinant of mobility at three months and one year. Savino et al. found that grip strength measured in hospital predicted recovery of walking ability in patients with hip fracture [13]. In contrast, our findings indicate that neither muscle mass nor grip strength, when analysed as continuous variables, were associated with change in mobility. This indicates that the choice of cut-points for low muscle mass or low grip strength would not have changed our results. We found an association between mobility pre-fracture and change in activities in daily living, but this was an exploratory analysis and the effect size was small.

Sarcopenia was associated with an increased probability of becoming a resident of a skilled nursing home (OR 3.2, 95% CI 0.9 to 12.4, $P = 0.048$) and the combined endpoint of becoming a resident of a nursing home or death (OR 3.6, 95% CI 1.2 to 12.3, $P = 0.02$). This is a clinically relevant finding but must be interpreted with caution, as it was an exploratory outcome and we were not able to correct for age, sex or BMI because of the low number of outcomes. Among the participants who had sarcopenia status determined, 6 participants died or became permanent residents of a nursing home among the not sarcopenic and 12 participants among those who were sarcopenic. The NMS was chosen as our measure of physical performance because we assumed that many participants would be unable to walk at inclusion. The NMS is extensively studied as a predictor of mobility, morbidity, mortality and becoming a resident of a nursing home [28–31]. We found a ceiling effect with the NMS, with 54% of participants scoring the maximum 9 before the fracture and 30% at one-year. Possibly because participants with a pre-fracture NMS of 0 or 1 were not eligible for inclusion. Patients found the NMS easy to understand and scoring was straightforward. Surprisingly, we found that 8% of patients had better mobility at one-year compared to pre-fracture. For some of the patients this was due to illness that started before the fracture, and their improvement in mobility after hip fracture was due to resolution of their illness, rather than successful rehabilitation. Use of rehabilitation services improves mobility after hip fracture [32, 33]. We did not record what rehabilitation services the participants received, and it is possible that rehabilitation could mediate the effect between sarcopenia and change in mobility.

The participants in our study were slightly younger (79.4 vs. 80.0 years) and had a lower mean ASA score (2.5 vs. 2.7) indicating better health compared to patients in the Norwegian Hip Fracture Register. We did not include



patients from skilled nursing homes or with severe cognitive impairment, and our results are not generalizable to those populations.

Anthropometry is considered a less valid method for determining muscle mass compared to dual-energy X-ray absorptiometry (DXA) or computed tomography scan [34]. The EWGSOP recommends not using anthropometry to determine muscle mass in research but allows for it in clinical practice [4]. We have previously investigated how anthropometry compares to DXA in identifying low muscle mass and found an area under the curve of 0.64 (95% CI 0.54–0.75) in women and 0.72

(95% CI 0.56–0.87) in men [35]. Using anthropometry to identify low muscle mass instead of DXA can lead to misclassification of muscle mass status and hence sarcopenia status. By using anthropometry to determine sarcopenia status we reduced our ability to detect an effect of sarcopenia on outcomes. We used anthropometry in our study because it is in common use [36], inexpensive, and more easily performed on patients with reduced mobility and acute illness, compared to DXA [37]. Some consider objectively measured physical performance superior to self-reported mobility, such as the NMS, but when the two types of measurement are compared in

Table 2 Outcomes after one year by sarcopenia status

	Marginal values						Regression (sarcopenic – not sarcopenic)					
	Not sarcopenic			Sarcopenic			Unadjusted			Adjusted		
	Mean	(SD)	No.	Mean	(SD)	No.	Estimate	95% CI	P	Estimate	95% CI	P
Change NMS	-1.2	(1.8)	n = 117	-1.3	(1.9)	n = 67	0.0	-0.6 to 0.6	0.9	0.2	-0.5 to 0.9	0.6
Change B-ADL	-0.8	(2.4)	n = 76	-2.2	(3.9)	n = 52	-0.4	-1.2 to 0.3	0.3	-0.3	-1.1 to 0.6	0.6
				Not Sarcopenic			Sarcopenic			OR	95% CI	P
Fracture, n (%) N				7	(6)	n = 120	8	(11)	n = 71	2.0	(0.6 to 7.0)	0.3
Hip fractures, n (%) N				3	(2)	n = 124	3	(4)	n = 77	1.6	(0.2 to 12.5)	0.7
Reoperations, n (%) N				7	(6)	n = 124	1	(1)	n = 77	0.2	(0.0 to 1.8)	0.2
Hospitalization, n (%) N				41	(33)	n = 123	24	(33)	n = 73	1.0	(0.5 to 1.9)	1.0
Nursing home, n (%) N				5	(4)	n = 124	9	(12)	n = 77	3.2	(0.9 to 12.4)	0.048
Death, n (%) N				3	(2)	n = 124	5	(6)	n = 77	2.8	(0.5 to 18.5)	0.3
Death or nursing home, n (%) N				6	(5)	n = 124	12	(16)	n = 77	3.6	(1.2 to 12.3)	0.02

Outcomes after one year by sarcopenia status (sarcopenic – not sarcopenic). Regression analysis for change in mobility and Barthel ADL from pre-fracture until one year adjusted for age, sex and BMI with imputation of missing values. ADL: Barthel Activities of daily living. Analysis for fracture, hip fracture, reoperations, all-cause hospitalization, nursing home, death or nursing home or death by two-sided Fisher's exact test using available cases. NMS: New mobility score. B-ADL: Barthel activities of daily living. OR: Odds ratio

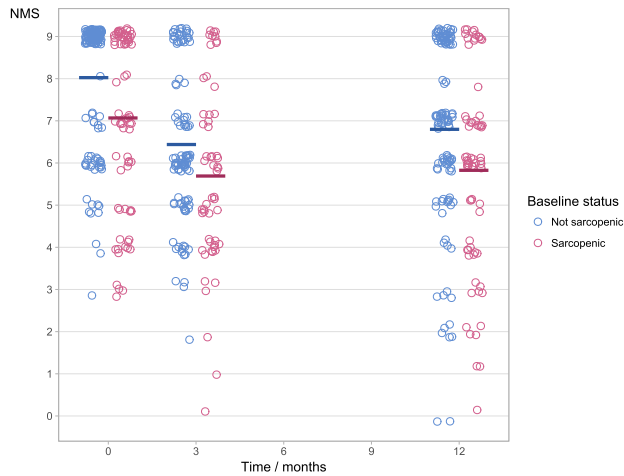


Fig. 3 New Mobility Score (NMS) during hospitalization, at three months, and at one year, stratified by sarcopenia status during hospitalization. The horizontal lines show mean NMS scores

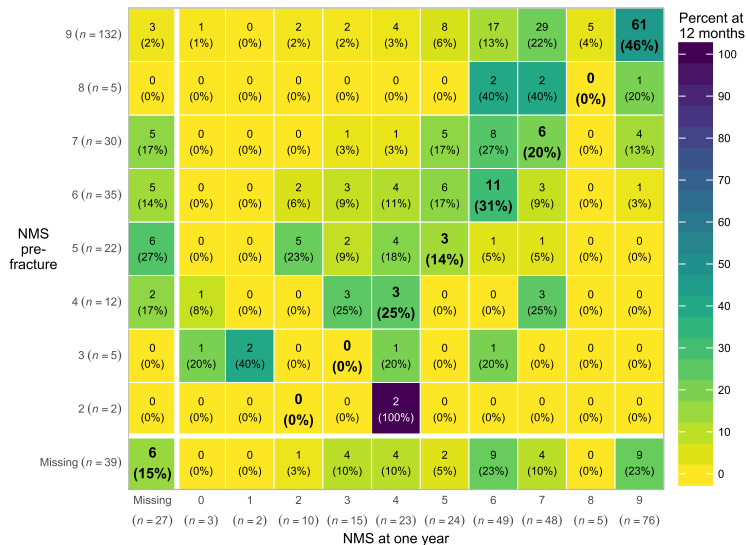


Fig. 4 New Mobility Score (NMS) pre-fracture and at one-year follow-up. The first number in each cell is the number of patients with the given combination of NMS scores. For each row, the percentage values and the cell shadings show the distribution of NMS at follow-up for a given NMS score at baseline. No patients had a NMS of 1 at baseline, and patients with a NMS score of 0 was excluded from the study. Patients with the same NMS score at baseline and follow-up are shown in boldface, and any cell to the right of this diagonal indicates an improvement in the NMS

Table 3 Outcomes after one year predicted by muscle mass, grip strength or mobility

	Unadjusted β (95% Confidence interval)			Adjusted β (95% Confidence interval)				
Change in New Mobility Score at one year								
ALM/height ² , kg/m ²	0.0	(-0.1 to 0.2)	p = 0.7	n = 175	0.2	(-0.1 to 0.4)	p = 0.2	n = 155
Grip strength, kg	0.0	(-0.0 to 0.0)	p = 0.7	n = 193	-0.0	(-0.0 to 0.0)	p = 0.7	n = 169
Change in Barthel activities of daily living at one year								
ALM/height ² , kg/m ²	0.0	(-0.2 to 0.3)	p = 0.8	n = 121	0.1	(-0.2 to 0.4)	p = 0.4	n = 115
Grip strength, kg	0.0	(-0.0 to 0.1)	p = 0.07	n = 137	0.0	(0.0 to 0.1)	p = 0.1	n = 128
New Mobility Score, point	0.2	(0.0 to 0.4)	p = 0.03	n = 148	0.2	(0.0 to 0.4)	p = 0.03	n = 130
Death or nursing home at one year								
ALM/height ² , kg/m ²	0.8	(0.6 to 1.2)	p = 0.3	n = 194	1.0	(0.6 to 1.7)	p = 1.0	n = 170
Grip strength, kg	0.9	(0.9 to 1.0)	p = 0.002	n = 222	0.9	(0.9 to 1.0)	p = 0.1	n = 186
New Mobility Score, point	0.7	(0.6 to 0.9)	p < 0.001	n = 243	0.8	(0.6 to 1.0)	p = 0.06	n = 194

Outcomes after one year by muscle mass, grip strength or mobility. Analysis of change in mobility and Barthel activities of daily living by regression and with imputation of missing values. ALM/height², grip strength and New Mobility Score are continuous, independent variables. Change in New Mobility Score and Barthel activities of daily living are continuous dependent variables. n: number of cases without missing values. OR: Odds ratio, ALM: Appendicular lean mass. Adjusted analysis with age, sex and BMI as covariates

hip fracture patients they have been found to be equally predictive of outcomes [38]. Future research on sarcopenia in hip fracture patients could explore other methods for determining sarcopenia, such as computed tomography to directly measure intramuscular adipose tissue [34] or using objective measures of physical performance such as the Short Physical Performance Battery [39]. A randomized controlled study of an intervention targeting sarcopenia status to improve mobility after hip fracture would provide additional insight on the causal relation between sarcopenia and mobility.

The included patients were a minority of all patients operated on for hip fracture during the period of inclusion. We included postoperative patients who were frequently bed-bound, receiving opiates for pain relief, with indwelling urinary catheters and while receiving intravenous fluid therapy. We believe there were three main reasons for the low recruitment rate: patients did not fulfill the inclusion criteria, patients were discharged before the consent process could be completed, and participants declined to participate because it was too much of a burden. For the patients who did consent to participate we found that determining sarcopenia by anthropometry, grip strength and the NMS was feasible. The greatest difficulty was in determining the height of the participants.

Conclusion

Sarcopenia status determined in postoperative hip fracture patients by anthropometry, grip strength and self-reported mobility did not predict change in mobility in the year after hip fracture. Sarcopenia was associated with having lower mobility at one year and a greater risk of becoming a resident of a nursing home or death.

Abbreviations

ALM: Appendicular lean mass; ASA: ASA Physical Status Classification System score; B-ADL: Barthel activities of daily living; BMI: Body mass index; CI: Confidence interval; DXA: Dual-energy X-ray absorptiometry; EWGSOP: European Working Group on Sarcopenia in Older Persons; NMS: New mobility score; OR: Odds ratio; SD: Standard deviation

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OMS, AHR, BB and CCG designed the study and wrote the study protocol. All authors have contributed to the manuscript, agree on submitting it for publication, and vouch for the integrity of the data and analysis. OMS and MHK have been responsible for including patients and data collection. OMS performed all data analyses except the regression analyses that used multiple imputation. AHR has been the project leader. KOH performed the regression analyses that used multiple imputation and prepared all the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the research committees at the participating hospitals (Haraldsplass Deaconess Hospital and Haukeland University Hospital, Bergen, and Diakonhjemmet Hospital, Oslo, Norway), the Regional Committee on Medical and Health Research Ethics (case 2011/1322/REK sør-øst B) and was conducted according to the principles of the Declaration of Helsinki. Participation was by written informed consent with participants receiving oral and written information on the first day and signed the consent form on a subsequent day.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway. ²Department of Clinical Science, University of Bergen, Bergen, Norway. ³Department of Rheumatology, Haukeland University Hospital, Bergen, Norway. ⁴Western Norway University of Applied Sciences, Bergen, Norway. ⁵Department of Orthopedics, Haukeland University Hospital, Bergen, Norway. ⁶Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. ⁷Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway. ⁸Department of Clinical Science, the Faculty of Medicine and Dentistry, University of Bergen, Postbox 7804, n-5020 Bergen, Norway.

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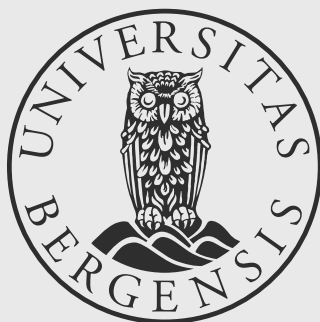
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