Prognostics of recovery in hip fracture patients

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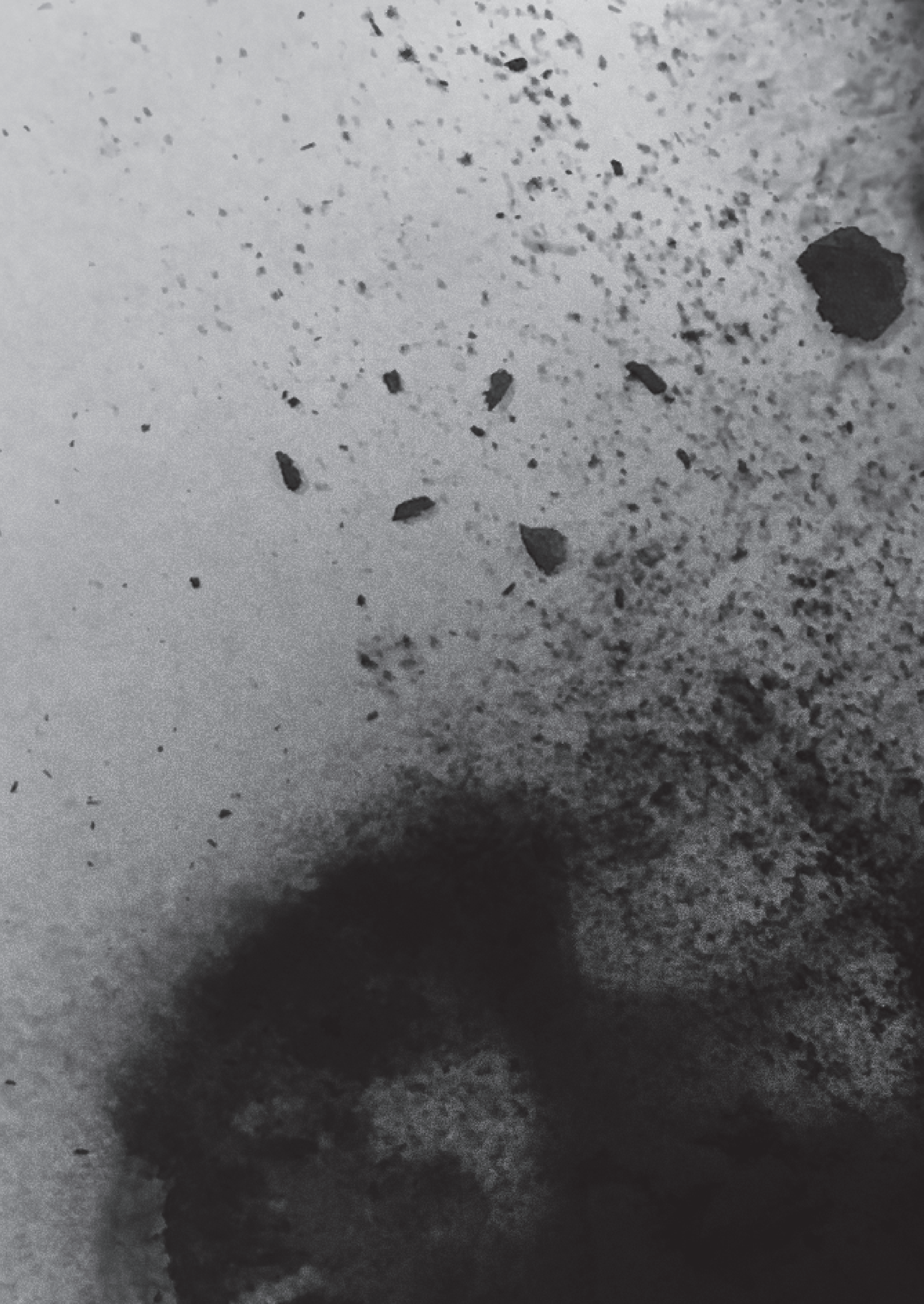
Title: Prognostics of recovery in hip fracture patients
Issue date: 2021-09-02



Chapter 7

Functional recovery: design of a cohort study

van der Sijp M.P.L., van Eijk M., Niggebrugge A.H.P., du Pré K.J., Gussekloo J., Slagboom P.E., Suchiman H.E.D., Blauw G.J., Achterberg W.P. Functional recovery in older patients with a proximal femoral fracture: design of a cohort study. *[submitted]*.

Abstract

Background: Proximal femoral fractures are usually fragility fractures following minor trauma. The long-term effects are severe with significant mortality and morbidity characterized by impaired mobility and independence. These adverse outcomes are often attributed to high age, prevalent comorbidities and diminished physiological reserves (often referred to as frailty) in a predominantly older patient population. The aim of this project is to identify patient-related prognostic factors and study their impact on functional recovery within one year after surgery in older patients with a proximal femoral fracture. This knowledge could improve prognostic accuracy and highlight new areas for intervention programs.

Methods and design: This observational inception cohort study will include patients with a proximal femoral fracture. The primary outcome is a composite outcome defined as meeting the following three criteria: survival, returning to a prefracture living situation and recovery of mobility within 1 year after surgery. Besides standard regression analyses, the application of multi-state models will be explored. Prognostic factors that will be related to the outcome include nutritional state, handgrip strength, prefracture mobility, prefracture functional independence and cognition. Blood will be collected and stored for biomarker quantification and exploration of additional prognostic values using high-throughput proton nuclear magnetic resonance spectroscopy. Patients will be treated according to the routine local care pathway.

Results: In 2017 a pilot population of 490 proximal femoral fractures were treated in the study hospital's hip fracture center, and included in a feasibility study. From this we estimated that approximately 186 patients will be eligible for inclusion annually, and unwillingness to participate is expected to be below 50%. Compared to the entire patient population, eligible patients were on average older, but with a more favourable ASA classification, better functionality, showed more independent living and more pertrochanteric femur fractures.

Discussion: This study uses a long-term composite outcome and will use both functional and biological prognosticators.

Background

Proximal femoral fractures in older patients are strongly associated with adverse outcomes, with only half of all patients returning to pre-fracture mobility levels.[1] Simultaneously, one-third of all previously community dwelling patients are permanently institutionalized[2] and one-year mortality rates are estimated to be around 25%.[3-5]

Various definitions have been proposed for functional outcome in patients with proximal femoral fractures, and different methods have been explored to assess it.[6] Different ways have been used to cope with the competing outcomes mortality and institutionalization when studying functional outcome.[7-9] Regarding these competing outcomes as failure to recover reflects the individuals' changes on a successful recovery. Alternatively, a novel method using multi-state models allows for analyses of individual transitions in a recovery process with multiple (competing) outcomes.[10] In addition, multi-state models can be used to prognose patient outcomes at any specific moment in the recovery process. The model can take into account the patient's prefracture characteristics, aspects of treatment and all prior transition rates.[11]

These methods could provide new insight in the functional prognosis of patients and the relevant prognostic factors. Various prognostic factors of functional recovery, especially short term, have been studied previously.[6] However, current prognostic accuracies remain poor and underlying mechanisms and mediators are still poorly understood[6]. The chief patient characteristics previously identified as prognostic factors for long-term functional outcomes include age[12-14], comorbidity[14-17], cognition[17-19] and prefracture functionality[12-14, 16]. While comorbidity and cognition fit well in a biopsychosocial model of health, age and prefracture function may be related to more basal underlying factors that define the patients' physiology.[20] These factors, however, have been little studied in proximal femoral fracture patients to date. Basic methods to define a patient's functional capacities could involve more physical measurements. In older patients sarcopenia, defined as a decreased muscle mass or muscle strength[21], is an important determinant of function.[22] Assessing muscle strength using handgrip strength (HGS) is an easy-to-use technique and strongly correlated with general and lower extremity muscle strength.[23] In patients with a proximal femoral fracture, HGS is an independent prognostic factor of long-term functional recovery.[24, 25] Alternatively, the fat free mass index (FFMI) can be used to measure muscle mass rather than strength. The FFMI is sometimes incorporated in malnutrition screening methods[26] as malnutrition is a major risk factor for sarcopenia and is prevalent in admitted older patients.[27] Consequently, malnourished patients with a proximal femoral fracture tend to have a slower recovery, poorer functional outcomes and a higher risk of mortality.[28] Although a strong correlation between muscle strength, muscle mass, nutritional status and the patients' functional capacity seems evident, their combined and independent effects on long-term functional recovery in patients with a proximal femoral fracture have not been studied in detail.

Besides these physical assessments, the plasma protein, albumin, is frequently studied and often considered an important marker of a patients' nutritional status. It is a prognosticator for mortality and adverse outcomes in various patient populations, including patients with a proximal femoral fracture.[29-31] It has also been identified as an independent prognostic factor of function in patients recovering from ischemic stroke.[32] Few other associations between the patients' health status and routine blood results or metabolic profiles have previously been studied for prognostic purposes in older patients.[31, 33] However, the circulatory metabolome may be a potentially novel, minimally-invasive indicator of morbidity and mortality risks as it holds numerous different metabolites that provide information on the health status of the patient and on specific organ systems. Biochemical assessment of health and (the risks for) comorbidity defines biological age, which may ultimately provide a more accurate prognosis than chronological age.[20, 34] Metabolomic profiles, composed of many different serum metabolite measurements, have mostly been studied in large, non-specific populations to find prognostic factors of all-cause mortality or the onset of specific diseases.[35] Due to practical and economic reasons these techniques have had a limited impact in clinical practice to date. The prognostic value of serum markers for long-term functional outcomes of older trauma patients specifically has not been studied previously.

We hypothesize that these biological type of assessments of the patients' health status will improve the prognostic accuracy of functional recovery. Because recovery from a proximal femoral fracture is regarded primarily as a physical process, this study will focus on patients' physical characteristics.

Objective

The aim of this study is to identify patient-related prognostic factors and study their impact on functional recovery within one year after surgery for older patients with a proximal femoral fracture. The study will mainly focus on the areas outlined in the research questions below:

- How do the patient characteristics nutritional state, HGS, prefracture mobility, prefracture independence in ADL and cognition affect functional recovery within 1 year in older patients with a proximal femoral fracture?
- Can preoperative metabolic profiling be used for prognostics of functional recovery in patients with a proximal femoral fracture?

Methods and design

This protocol and the study accord with to the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' statement guidelines for reporting observational studies.[36] Recruitment all consecutively admitted patients with a proximal femoral fracture (AO-classification 31A/B)[37] started in December 2018 at the level 1 trauma teaching hospital 'Haaglanden Medical Center' (HMC) in The Hague. Detailed in- and exclusion criteria are presented in Table 1. Eligibility for inclusion is assessed during admission by the research staff. The project is titled 'Hip fractures: Inventorization of Prognostic factors and their Contribution towArds Rehabilitation in older pErsons' (HIP CARE).

Table 1. Inclusion and exclusion criteria for eligible study subjects.

Inclusion criteria	Exclusion criteria
Age ≥70 years	Pre-fracture residence in a nursing home
Unilateral fracture (AO type 31 A1-B3)	Pathological fractures
Eligible for (geriatric) rehabilitation	Severe cognitive impairment
	Insufficient in the Dutch language

The eligibility assessment is performed by a combined assessment of the patient charts and patient and/or caregiver interviews. Eligibility for (geriatric) rehabilitation is assessed weekly in a multidisciplinary team meeting and generally considered for patients who do not permanently reside in a nursing home. Severe cognitive impairment is defined as a 6CIT ≥11 upon admission or an official diagnosis of dementia.

Outcomes

All outcomes are assessed during check-ups at 6 weeks, 3 months and 1 year after surgery. These are routine check-ups offered to all patients with proximal femoral fractures admitted to the Haaglanden Medical Center in The Hague, in accordance with a protocolled local care pathway.

Assessment of the primary outcome

The primary outcome of this study is the rate of successful recovery within one year after surgery, as defined by the combination of patient survival, a return to the prefracture living situation and recovery of mobility. These criteria are adaptations of the Tier 1 healthcare outcomes defined by Porter et al. (2010), which should be considered the most basic and important outcomes for all healthcare, and with significant socio-economic impact.[38] Patients who meet all three criteria simultaneously at any point within the first year after admission (at 6 weeks, 3 months and 1 year) will be considered to have recovered successfully.

- *Patient survival* will be assessed using observed mortality, defined as death due to any cause. The time-to-event will be calculated based on the time of arrival in the emergency department.
- The *living situation* will be defined as the patients' residence registered during admission (the patients' prefracture living situation), at discharge (the discharge location) and at follow-up (6 weeks, 3 months and 1 year after surgery). The living situation will be categorized binomi-

ally based on the self-dependency of the patient. Patients either live independently (at home, either with or without professional homecare or in a residential home) or are permanently institutionalized in a nursing home (for long-term care). In terms of the primary outcome, success is considered as not permanently residing in a nursing home.

- *Mobility* will be scored using the Parker Mobility Score (PMS, also: New Mobility Score). This tool rates the use of an aid or assistance in three categories of ambulation, with 4 possible options covering an outcome range of 0-9.[39] The PMS was developed specifically for patients with a proximal femoral fracture and has been shown to be a reliable and valid prognosticator of functional (rehabilitation) outcomes.[39, 40] The tool has a high relative and absolute inter-tester reliability and little recollection bias when used to assess prefracture mobility.[41] The PMS will be assessed and recorded during admission (as the patients prefracture mobility) and at each follow-up (6 weeks, 3 months and 1 year after surgery). Return to the individual prefracture level of mobility (follow-up PMS ≥ prefracture PMS) will be considered successful.

Secondary outcomes

- The individual outcomes which constitute the combined primary outcome (patient survival, living situation and mobility) will be considered as single secondary outcomes.
- Short-term assessments of the primary outcome will be measured at the 6 weeks and 3 months follow-up after surgery.
- Additional aspects of functionality will be assessed using a functional performance battery which includes Functional Ambulation Categories (FAC), the Short Physical Performance Battery (SPPB), as well as patient-reported assessments (the Katz Index of Independence in Activities of Daily Living (Katz-ADL) and the previously described PMS) at 6 weeks, 3 months and 1 year after surgery. The performance battery will be assessed during follow-up only when safe for patients. Patients with a FAC score ≥3, which implies need for continuous or intermittent support during ambulation[42], will not be assessed. The patient-reported assessments (Katz-ADL and PMS) will be evaluated for all patients during admission (considered as the patients' prefracture functionality) and at follow-up.
    - The Katz-ADL consists of 6 yes/no questions related to the patients' self-dependence in general activities of daily living.[43] It is a common indicator of a patient's dependency and is part of the Dutch quality indicator for proximal femoral fractures (DHFA).[44]
    - The Functional Ambulation Categories (FAC) score is a 6-point scale that facilitates assessment of independence in ambulation through observation of the patient.[42]
    - The Short-Physical-Performance-Battery (SPPB) is an objective tool assessing balance, walking speed and strength through a series of exercises.[45] Outcome scores are categorized into '≤3' (severe disability), '4-9' (high risk of developing a disability) and '>9' (low risk).[46]

Patients who are unable to perform the assessments are assigned to the first category for the analyses.

- Readmission and reoperation up to 1 year after surgery.
- Delirium as diagnosed by the hospital psychiatrist using DSM-V criteria. When a patient is admitted, delirium risk is routinely assessed by ward nurses using the (Dutch) VMS theme 'Frail Elderly'.[47] Patients with an elevated delirium risk and patients with a low clinical suspicion of delirium are screened three times daily by trained nurses using the Delirium Observation Screening Scale (DOS) scores.[48] When delirium is suspected, the hospital psychiatrist is consulted for diagnosis and treatment.
- Quality of life (QOL) will be registered retrospectively during admission as the prefracture QOL and at 6-weeks, 3-months and 1-year outpatient follow-up using the Dutch version of the 5-dimensional EuroQol (EQ-5D-5L).[49]

Baseline parameters

The independent association of the following baseline characteristics (exposures) and the primary outcome will be assessed: nutritional state, HGS, prefracture mobility, prefracture independence in ADL and cognition.

- Nutritional state will be assessed using the Mini Nutritional Assessment Short-Form (MNA-SF). This nutritional screening tool is the most widely used tool in both literature and clinical settings, is designed for older patients and has been extensively validated in proximal femoral fracture patients.[50] It combines five questions concerning food intake, weight loss, mobility, psychological stress and acute disease or neuropsychological problems with the BMI and/or FFMI. Patients with a MNA-SF score of 12-14 points are considered normal, patients with 8-11 points are considered 'at risk of malnutrition' and patients with 7 points or less are considered 'malnourished'.[50, 51]
  - o BMI is calculated using patient weight and height ([weight] / [height]^2). The patients' weight will be measured during admission in the emergency department when patients are transferred to the hospital bed using a ceiling-mounted lifter with built-in scale. The patients' height will be measured in upright position or using the lower-leg method at the second outpatient clinical assessment.
  - o The FFMI will be measured during admission using a single-frequency Bioelectrical Impedance Analysis (BIA) device (the Bodystat®500 by Bodystat Ltd).
- Handgrip strength (HGS) will be assessed during admission and at the second follow-up, three months after admission, using a Jamar handheld dynamometer (Lafayette Instrument Co). The highest force (measured in whole kilograms) out of three consecutive measurements with the dominant hand will be registered and used for analysis. Measurements are categorized as normal or abnormal based on reference values stratified for age and sex.[52]

- Prefracture independence in ADL will be assessed using the Katz-ADL and prefracture mobility using the PMS of the period immediately before the fall.
- Using the Six Item Cognitive Impairment Test (6CIT), cognition will be rated in the emergency department during admission for all patients admitted without a previously known diagnosis of (any form of) dementia. Patients will be classified as cognitively impaired if they have a known diagnosis of dementia or a 6CIT score of ≥11.[53]

The following study parameters will be assessed during admission and included as potential confounders in the analyses: age, sex, general health score (using the ASA classification)[54], prefracture fear of falling (using the 1-item fear of falling (FOF)[55] during admission), fracture type, type of surgery (prosthesis or osteosynthesis) and perioperative anesthesia types (including preoperative Fascia Iliaca Compartment Blocks and either an intrathecal block with or without spinal morphine or general anesthesia during surgery).

Complications will be grouped and registered at discharge and at follow-up. Most have been described previously by van der Sijp et al. (2017).[56]

- Surgical complications (postoperative bleeding, postoperative bleeding, implant failure, implant dislocation, implant luxation, femoral head necrosis, periprosthetic fractures, superficial wound infection, deep wound (prosthesis) infection, nerve damage).
- Non-surgical complications (anaemia (Hb<6.0), cardiac complications (including decompensation, ischemia and arrhythmia), stroke, pressure sores, electrolyte disturbances, gastrointestinal bleeding, ileus, obstipation, ulcers, chronic obstructive pulmonary disease (COPD) exacerbations, pulmonary embolism, pneumonia, respiratory insufficiency, renal function disorders, sepsis, thrombosis, phlebitis, urinary tract infections, urinary retention, falling with or without a new fracture).

Blood samples

During admission blood will be obtained from the emergency department via a venepuncture for routine preoperative blood work. The routine blood tests include the sedimentation rate, erythrocytes, haemoglobin, haematocrit, leukocytes, thrombocytes, leukocyte differentiations, sodium, potassium, calcium, phosphate, creatinine, glomerular filtration rate, albumin, alkaline phosphates, glucose, thyroid stimulating hormones, free T4, parathyroid hormone, vitamin D and CRP.

After routine tests, residual blood (EDTA and heparin) will be prepared for long-term storage at -80°C. Until stored, all blood samples will be handled and tested only by the clinical laboratory of the study hospital. The stored blood will be used for biomarker quantification using high-throughput proton nuclear magnetic resonance (NMR) spectroscopy (Nightingale Ltd, Helsinki, Finland). This method provides simultaneous quantification of circulating lipid concentrations, lipoprotein subclasses, proteins, low molecular weight metabolites (including amino acids, fatty acids and ketone bodies and glycolysis precursors) and other small molecules. Outcomes are expressed in specific lipoprotein- and fatty acid composite scores and absolute molar concentration units. Details of experimentation and application of the NMR metabolomics platform have been given previously in various epidemiological cohort studies.[29, 35, 57-59]

Usual care and procedures

All assessments denoted in table 2 with an 'A' and all treatment aspects described below (unless otherwise specified) have been part of routine care for all patients (admitted with an AO-classification 31A/B fracture) since December 21, 2016 and are documented in the local care pathway protocol of the hip fracture center (HFC) at the Haaglanden Medical Center.

Table 2. Timeline for all routine and study procedures and assessments.

Procedure/Assessment	Admission	In-hospital treatment phase	6 weeks after surgery	3 months after surgery	12 months after surgery
PMS	A[f]		A	A	A
Living situation	A		A	A	A
Survival			A	A	A
Baseline measurements	A				
Blood samples	A	A			
Katz ADL	A[f]		A	A	A
EQ-5D-5L	A[f]		A	A	A
6CIT	A		A	A	A
Nutritional screening[d]	A				
FFMI	B			B	
HGS	B			B	
NRS pain		A	A	A	A
Complications[b]		A	A	A	A
FOF[e]	A[f]		A	A	A
Functional performance battery[c]			A	A	A
X-ray assessment	A	A	A[b]	A[b]	

A. Routine assessments for standard care. B. Additional assessments for study purposes.
[a] For osteosyntheses only. [b] Any patient-reported complication in the previously described surgical and non-surgical complication list and any reason for a postoperative readmission to a hospital. [c] Short physical performance battery (SPPB), Functional Ambulation Categories (FAC). [d] SNAQ score and MNA-SF. [e] Fear of Falling; 1-item FOF during admission and Falls Efficacy Scale (FES) i7 at outpatient follow-ups. [f] Assessment of the prefracture situation. ADL activities of daily living, EQ-5D-5L 5-level 5-dimensional EuroQol, 6CIT Six Item Cognitive Impairment Test, FFMI fat free mass index, HGS handgrip strength, NRS numeric rating scale.

Usual care during admission

Patients admitted with a suspected proximal femoral fracture will be examined in the trauma bay of the emergency department. The admission will be coordinated by the resident on call, after consultation with the trauma- or orthopaedic surgeon on duty. Cognitive and malnutrition screenings will be conducted using the 6CIT and the SNAQ score. For older patients (≥70 years) geriatric specialists will be consulted for co-treatment. Surgery of the fracture will be performed by a combined trauma-unit consisting of trauma- and orthopaedic surgeons, preferably within 24 hours. After surgery, patients will reside on a surgical ward dedicated to proximal femoral fracture patients. Patients will be visited daily during rounds by the ward doctor, a surgeon and a senior nurse. Twice weekly all patients will be discussed in a multidisciplinary team meeting that includes the trauma- or orthopaedic surgeon, ward doctor, geriatrician, ward nurse, physiotherapist, dietician and transfer nurse. The common goal is an uncomplicated recovery, with discharge 3 days after surgery to an appropriate rehabilitation setting.

Usual care during outpatient visits

The appropriate rehabilitation setting after discharge will also be discussed during the multidisciplinary team meetings. Patients who did not permanently reside in a nursing home before admission and are eligible for rehabilitation programs (either at home or in a rehabilitation nursing home) will be invited to visit the multidisciplinary outpatient clinic at 6 weeks, 3 months and 1 year after surgery. During these visits patients will be invited to see the doctor's assistant, a physiotherapist, the geriatrician (for patients 70 years and older) and a trauma or orthopaedic surgeon. The various specialists focus on the patient's functionality, fracture healing, complications, osteoporosis screening, fall prevention and general quality of life. The eligibility criteria for the multidisciplinary outpatient clinic visits apply for each subsequent outpatient visit and are briefly reassessed and discussed by the specialists during each outpatient visit. Patients participating in the study who do not attend the outpatient clinic for any reason will be contacted to offer a home visit by one of the researchers for the collection of solely the study data.

The assessments performed during routine outpatient visits cannot be performed in cognitively impaired and non-ambulatory patients, as transport to the hospital and the outpatient visit is considered too burdensome. Instead, these patients will be called by phone for clinical assessment (either with the patient or a caregiver) at 6 weeks, 3 months and 1 year after surgery.

A pilot of this extensive follow-up regime started on January 1, 2017 and included approximately half (n=267) of the proximal femoral fracture patients admitted in 2017. Selection was based on certain weekdays and excluded patients operated on Saturday, Sunday and Wednesday. As of January 1, 2018, the extensive follow-up was available to all (approximately 500) patients with a proximal femoral fracture.

Data registration

Starting on December 21, 2016, all patients admitted to the HMC with a proximal femoral fracture are registered in an external, coded database. Data are collected prospectively, simultaneously with the clinical notes in the original patient files taken during admission and all follow-up by various medical personnel.[56] The database is used for national registration, internal quality of care checks and scientific purposes.[44] The methodology of this data collection and of any subsequent observational studies has been approved by the institutional Medical Research Ethics Committee (METC Southwest Holland, protocol number 18-029). Patients are offered an opt-out for data collection during admission. Explicit patient permission was considered unnecessary by the ethics committee due to the observational nature of the routine data collection.

In addition to this routine data collection, a subset of data is collected for the research purposes of this study only (denoted with the letter B in table 2). These data are collected by research staff only, and stored in a separate coded and anonymized database. Additional ethical approval was obtained for this data subset from the same institutional Medical Research Ethics Committee (METC Southwest Holland, protocol number 18-081; NL66871.098.18). Written informed consent was obtained from all patients included in this section of the data collection. All patient data are handled according to Good Research Practice guidelines.

Statistical analysis plan

Patient characteristics and treatment aspects will be described using summary statistics and compared by univariable analysis. Missing data will be analyzed for patterns (not at random, at random, completely at random). Data missing at random will be imputed using multiple imputation techniques. Categorical data will be compared using the chi-squared test or Fisher's exact test if numbers are insufficiently large (expected cell counts >5). The unpaired two-sample t-test will be used for continuous data with a normal distribution (reported with standard deviations), and the Mann–Whitney U test for non-normal distributions (Kolmogorov-Smirnov test of $p< 0.05$, reported with interquartile ranges, IQR).

The main analysis of this study assesses the associations between the exposures (nutritional state, HGS, prefracture mobility, prefracture independence in ADL and cognition) and the primary outcome (functional recovery) while considering potential confounding factors. The primary outcome will be analyzed using regression analyses, assessing the associations between exposures and the outcome. Correlation coefficients will be calculated for all selected variables to check for multicollinearity ($r > 0.8$) using Spearman rank-order correlation methods for monotonic relationships, or ordinal variables and the Pearson product moment correlation for linear relationship between continuous variables. To prevent overfitting, the one-in-ten rule will be applied to determine how many prognostic factors can be derived from data in the multivariable analysis.[60, 61] A multi-state model, which includes the competing events of not returning to an independent form of living, or dying, will be used to explore patient transitions throughout the recovery process. Reasons for failure to follow up will be recorded and compared between the cohorts.

The metabolomic outcomes will be examined and if skewed LN-transformed to obtain normal distributions. A value of one will be added to all metabolites for which the value is below the detection limit. We will first base univariate analysis on all 226 available measurements and the novel scores we have previously generated from this platform.[62] Due to the high correlation among the measurements, the selection of independently associated metabolites will be based on a subset of metabolites to prevent overfitting, or principal component analysis (PCA) will be applied to reduce data dimensions.

A p-value below 0.05 ($p < 0.05$) will be considered statistically significant for all outcomes. All statistical analyses will be performed using IBM SPSS statistics software for Windows version 25.0.

Sample size

No data are available on the combined outcome measure proposed in this manuscript. A recent study by Helminen et al. (2017) explores the effect of nutritional status on the recovery of mobility and mortality at 1 year after surgery. These are two of the three components of our combined outcome.[7] Here, the response rate of unsuccessful recovery to prefracture levels of mobility for patients with normal nutritional scores was 48% (of this group, 16% died and of the surviving patients 32% did not recover their mobility). The response rate of unsuccessful recovery to prefracture levels of mobility for patients with abnormal nutritional scores was 84% (of this group, 37% died and of the surviving patients 47% did not recover their mobility).

A logistic regression of the binary response variable (nutritional status) on the binary independent variable (recovery of mobility) with a sample size of 84 observations (of which 67% are in the malnourished group and 33% are in the control group) achieves 79% power at a 0.05 significance level to detect a change in Prob(Y=1) from the baseline value of 0.84 to 0.48. This change corresponds to an odds ratio of 0.176. An adjustment was made since a regression analysis of the independent variable of interest on the independent variable prefracture mobility (which was considered the most significant covariate) in the logistic regression obtained an R-Squared of 0.340 (using the feasibility data). Anticipating loss to follow-up of up to 40% due to incompliance and drop out, inclusion of at least 140 patients is required.

A limitation of this power calculation is that the effect of the third component of our combined outcome (return to prefracture living situation) is ignored.

Table 3. Characteristics of all patients admitted in 2017 and those eligible for inclusion.

Patient characteristic	All patients n=267 (%)	Eligible patients n=113 (42.3%)	P-value
Mean age (SD)	78.9 (14.0)	83.9 (6.9)	*<0.001*
Sex (f)	182 (68.2)	80 (70.8)	0.429
ASA classification			
I	16 (6.1)	2 (1.8)	
II	110 (42.1)	56 (51.4)	
III	120 (46.0)	46 (42.2)	
IV	14 (5.4)	5 (4.6)	
V	1 (0.4)	0 (0.0)	*0.027*
Cognitively impaired[a]	85 (32.4)	0 (0.0)	*<0.001*
MNA-SF			
14-12			
<12			
Katz-ADL			
0-2	188 (73.7)	101 (89.4)	
3-4	43 (16.9)	11 (9.7)	
5-6	24 (9.4)	1 (0.9)	*<0.001*
Living situation			
Independent	149 (55.8)	158 (75.2)	
Homecare	48 (18.0)	38 (18.1)	
Residential home	13 (4.9)	25 (5.1)	
Nursing home	49 (18.3)	0 (0.0)	
Rehabilitation home	3 (1.1)	2 (1.8)	
Other	5 (1.9)	1 (0.9)	*<0.001*
Fracture type			
FNF	155 (58.1)	57 (50.4)	
PFF	112 (41.9)	56 (49.6)	*0.031*
Treatment			
Prosthesis	102 (38.2)	43 (38.1)	
Osteosynthesis	162 (60.7)	70 (61.9)	
Conservative	3 (1.1)	0 (0.0)	0.324

SD standard deviation, f female, ASA American Society of Anesthesiologists, [a] assessed using the 6CIT score (≥11) or a previous diagnosed form of dementia, MNA-SF Mini Nutritional Assessment - Short Form, ADL activities of daily living, FNF femoral neck fracture, PFF pertrochanteric (and subtrochanteric) femur fracture, *italics* indicate statistical significance.

Feasibility study

Between January 1, 2017 and January 1, 2018, 487 patients were treated in the HFC for 490 proximal femoral fractures. Three patients were admitted with a second, contralateral fracture. Prospectively collected data on the admission were available for all patients, but extensive follow-up data (at 6 weeks, 3 months and 1 year) were only available for 267 of the fracture admissions included in the pilot group, which are presented here in a feasibility study. The mean age of the pilot population was 78.9 years (SD ±14.0) and the majority (68.2%) was female (table 3). A severe cognitive impairment (defined as a 6CIT ≥11 upon admission or an official diagnosis of dementia) was present in 85 patients (32.4%) during admission. Of the pilot population admitted in 2017, 113 (42.3%) would have been eligible for the current study because they had no cognitive impairment and were community dwelling, factors which constitute the main inclusion criteria for HIP CARE (table 3). These patients were on average older (because of the age selection criterion), but with a more favourable ASA classification, better functionality, more independent living and more pertrochanteric femur fractures than the general population. Within this potential inclusion population there was an in-hospital mortality rate of 4.4% and a 1-year mortality rate of 16.8% (table 4). From this we extrapolate an estimated potential sample size of 211 patients of whom 186 are expected to complete the 1-year follow-up, based on 500 admitted patients with a proximal femoral fracture per year. Missed inclusions due to logistical reasons, unwillingness to participate and discontinuation of follow-up in this older patient population are together estimated at no more than 50%. This anticipated inclusion of 93 patients annually would satisfy the required minimum of 140 patients within two years' time.

Table 4. Living situation of eligible patients before and after admission.

Living situation	Admission	Discharge	6 weeks	3 months	1 year
Independent	79 (69.9)	4 (3.5)	26 (23.0)	40 (35.4)	45 (39.8)
Homecare	27 (23.9)	8 (7.1)	26 (23.0)	38 (33.6)	27 (23.9)
Residential home	4 (3.5)	2 (1.8)	2 (1.8)	4 (3.5)	5 (4.4)
Nursing home	0 (0.0)	3 (2.7)	5 (3.4)	6 (5.4)	10 (8.8)
Rehabilitation home	2 (1.8)	91 (80.5)	42 (37.2)	10 (8.8)	3 (2.7)
Other	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mortality	-	5 (4.4)	9 (8.0)	11 (9.7)	19 (16.8)
Unknown	-	-	3 (2.7)	4 (3.5)	4 (3.5)

Discussion

Hip fractures are a major cause of mortality, institutionalization, reduced mobility, functional decline, informal care giver burden and reduced quality of life in older patients. Although the overall quality of emergency medicine, surgical procedures and post-acute care has improved, the functional prognosis of this specific group is still poor.[63] This poor prognosis is in part explained by the underlying causes of falls and fractures: the toll taken by a combination of chronic and acute geriatric syndromes and symptoms. Combinations of sarcopenia, osteopenia, malnutrition, comorbidity, polypharmacy, chronic infection, and cognitive decline are probably also responsible for the poor prognosis. However, although many prognostic studies have been performed, most looked at mortality only or used relatively short-term functional outcomes. Very few studies used a combined measure for success, and therefore excluded patients with an incomplete follow-up due to mortality.[13, 15, 64] Another weakness of many prognostic studies is the lack of a good description of the usual care given, which makes interpretation and extrapolation to clinical practice relatively complicated. In addition, many of the older usual care situations are potentially suboptimal, as there has recently been a shift towards treatment in orthogeriatric units. The vast majority of data is collected as part of the routine registrations by medical personnel instead of research staff, which may also reduce observer bias.

This study is unique in that it uses both short- and long-term outcomes (1-year), uses a composite primary outcome which is relevant to the patient and society, and studies a combined set of patient characteristics including among others metabolomics, an approach that has not been done previously in this patient population. This study aims to include all community dwelling patients aged 70 and above admitted with a proximal femoral fracture, for whom functional recovery of independence in the activities of daily living will have a major impact, both on them personally and on society in economic terms. As indicated by the feasibility study, these patients, who lived independently and have no or a minor cognitive impairment, are expected to have a more favourable ASA classification and baseline functionality. However, severe complications and mortality during admission might further favour the fitter patients for inclusion due to the challenge of obtaining informed consent.

Integrated care strategies have already been shown to produce improvements in physical, nutritional and sarcopenia status among community-dwelling elders.[65] This indicates a better understanding of these characteristics and additional targeting of care to this patient group may further improve treatment outcomes. The outcomes of this study provide additional information that can provide building blocks for future comprehensive improvements for these integrated care strategies.

Limitations

Limitations inherent to observational cohort studies do apply. All patients with severe cognitive impairment, and those previously institutionalized are excluded. Although these represent a minority of all hip fracture patients, this exclusion criterium limits the generalizability of all findings. However, this study aims to study factors relevant for functional recovery in patients who are eligible for (geriatric) rehabilitation.

The use of a composite outcome and novel analyses such as the multi-state model limits comparison across the existing evidence base.

Study status

Inclusion of patients and data collection began on December 20, 2018. Inclusion is ongoing and is expected to be completed in 2021, with the complete one-year follow-up available in 2022.

Reference list

1. Vochteloo AJ, Moerman S, Tuinebreijer WE, et al. More than half of hip fracture patients do not regain mobility in the first postoperative year. *Geriatr Gerontol Int*. 2013; 13: 334-41.
2. Vochteloo AJ, van Vliet-Koppert ST, Maier AB, et al. Risk factors for failure to return to the pre-fracture place of residence after hip fracture: a prospective longitudinal study of 444 patients. *Arch Orthop Trauma Surg*. 2012; 132: 823-30.
3. Abrahamsen B, van Staa T, Ariely R, Olson M and Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int*. 2009; 20: 1633-50.
4. Katsoulis M, Benetou V, Karapetyan T, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. *J Intern Med*. 2017; 281: 300-10.
5. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010; 152: 380-90.
6. Sheehan KJ, Williamson L, Alexander J, et al. Prognostic factors of functional outcome after hip fracture surgery: a systematic review. *Age Ageing*. 2018; 47: 661-70.
7. Helminen H, Luukkaala T, Saarnio J and Nuotio M. Comparison of the Mini-Nutritional Assessment short and long form and serum albumin as prognostic indicators of hip fracture outcomes. *Injury*. 2017; 48: 903-8.
8. Hannan EL, Magaziner J, Wang JJ, et al. Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. *JAMA*. 2001; 285: 2736-42.
9. Ingemarsson AH, Frandin K, Mellstrom D and Moller M. Walking ability and activity level after hip fracture in the elderly--a follow-up. *J Rehabil Med*. 2003; 35: 76-83.
10. Putter H, Fiocco M and Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007; 26: 2389-430.
11. Putter H, van der Hage J, de Bock GH, Elgalta R and van de Velde CJ. Estimation and prediction in a multi-state model for breast cancer. *Biom J*. 2006; 48: 366-80.
12. Cornwall R, Gilbert MS, Koval KJ, Strauss E and Siu AL. Functional outcomes and mortality vary among different types of hip fractures: a function of patient characteristics. *Clin Orthop Relat Res*. 2004: 64-71.
13. Hannan EL, Magaziner J, Wang JJ, et al. Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. *JAMA*. 2001; 285: 2736-42.
14. Moerman S, Mathijssen NM, Tuinebreijer WE, Nelissen RG and Vochteloo AJ. Less than one-third of hip fracture patients return to their prefracture level of instrumental activities of daily living in a prospective cohort study of 480 patients. *Geriatr Gerontol Int*. 2018; 18: 1244-8.
15. Osnes EK, Lofthus CM, Meyer HE, et al. Consequences of hip fracture on activities of daily life and residential needs. *Osteoporos Int*. 2004; 15: 567-74.
16. Beloosesky Y, Weiss A, Manasian M and Salai M. Handgrip strength of the elderly after hip fracture repair correlates with functional outcome. *Disability & Rehabilitation*. 2010; 32: 367-73.
17. Jones CA, Jhangri GS, Feeny DH and Beaupre LA. Cognitive status at hospital admission: Postoperative trajectory of functional recovery for hip fracture. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*. 2017; 72: 61-7.
18. Pajulammi HM, Pihlajamaki HK, Luukkaala TH and Nuotio MS. Pre- and perioperative predictors of changes in mobility and living arrangements after hip fracture--a population-based study. *Arch Gerontol Geriatr*. 2015; 61: 182-9.
19. Penrod JD, Litke A, Hawkes WG, et al. The association of race, gender, and comorbidity with mortality and function after hip fracture. *J Gerontol A Biol Sci Med Sci*. 2008; 63: 867-72.
20. Jackson SH, Weale MR and Weale RA. Biological age--what is it and can it be measured? *Arch Gerontol Geriatr*. 2003; 36: 103-15.

21. Cruz-Jentoft AJ. Beta-Hydroxy-Beta-Methyl Butyrate (HMB): From Experimental Data to Clinical Evidence in Sarcopenia. *Curr Protein Pept Sci*. 2018; 19: 668-72.

22. Larsson L, Degens H, Li M, et al. Sarcopenia: Aging-Related Loss of Muscle Mass and Function. *Physiol Rev*. 2019; 99: 427-511.

23. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol (1985)*. 2003; 95: 1851-60.

24. Di Monaco M, Castiglioni C, De Toma E, Gardin L, Giordano S and Tappero R. Handgrip strength is an independent predictor of functional outcome in hip-fracture women: a prospective study with 6-month follow-up. *Medicine (Baltimore)*. 2015; 94: e542.

25. Savino E, Martini E, Lauretani F, et al. Handgrip strength predicts persistent walking recovery after hip fracture surgery. *Am J Med*. 2013; 126: 1068-75.

26. Valentini A, Federici M, Cianfarani MA, Tarantino U and Bertoli A. Frailty and nutritional status in older people: the Mini Nutritional Assessment as a screening tool for the identification of frail subjects. *Clin Interv Aging*. 2018; 13: 1237-44.

27. Pierik VD, Meskers CGM, Van Ancum JM, et al. High risk of malnutrition is associated with low muscle mass in older hospitalized patients - a prospective cohort study. *BMC Geriatr*. 2017; 17: 118.

28. Miu KYD and Lam PS. Effects of Nutritional Status on 6-Month Outcome of Hip Fractures in Elderly Patients. *Ann Rehabil Med*. 2017; 41: 1005-12.

29. Bohl DD, Shen MR, Hannon CP, Fillingham YA, Darrith B and Della Valle CJ. Serum Albumin Predicts Survival and Postoperative Course Following Surgery for Geriatric Hip Fracture. *J Bone Joint Surg Am*. 2017; 99: 2110-8.

30. Mizrahi EH, Fleissig Y, Arad M, Blumstein T and Adunsky A. Admission albumin levels and functional outcome of elderly hip fracture patients: is it that important? *Aging Clin Exp Res*. 2007; 19: 284-9.

31. Laulund AS, Lauritzen JB, Duus BR, Mosfeldt M and Jorgensen HL. Routine blood tests as predictors of mortality in hip fracture patients. *Injury*. 2012; 43: 1014-20.

32. Nair R, Radhakrishnan K, Chatterjee A, Gorthi SP and Prabhu VA. Serum Albumin as a Predictor of Functional Outcomes Following Acute Ischemic Stroke. *J Vasc Interv Neurol*. 2018; 10: 65-8.

33. Ritt M, Jager J, Ritt JI, Sieber CC and Gassmann KG. Operationalizing a frailty index using routine blood and urine tests. *Clin Interv Aging*. 2017; 12: 1029-40.

34. Jylhava J, Pedersen NL and Hagg S. Biological Age Predictors. *EBioMedicine*. 2017; 21: 29-36.

35. Fischer K, Kettunen J, Wurtz P, et al. Biomarker profiling by nuclear magnetic resonance spectroscopy for the prediction of all-cause mortality: an observational study of 17,345 persons. *PLoS Med*. 2014; 11: e1001606.

36. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007; 370: 1453-7.

37. Kellam JF, Meinberg EG, Agel J, Karam MD and Roberts CS. Introduction: Fracture and Dislocation Classification Compendium-2018: International Comprehensive Classification of Fractures and Dislocations Committee. *J Orthop Trauma*. 2018; 32 Suppl 1: S1-S10.

38. Porter ME. What is value in health care? *N Engl J Med*. 2010; 363: 2477-81.

39. Parker MJ and Palmer CR. A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br*. 1993; 75: 797-8.

40. Kristensen MT, Foss NB and Kehlet H. [Timed Up and Go and New Mobility Score as predictors of function six months after hip fracture]. *Ugeskr Laeger*. 2005; 167: 3297-300.

41. Kristensen MT, Bandholm T, Foss NB, Ekdahl C and Kehlet H. High inter-tester reliability of the new mobility score in patients with hip fracture. *J Rehabil Med*. 2008; 40: 589-91.

42. Spilg EG, Martin BJ, Mitchell SL and Aitchison TC. A comparison of mobility assessments in a geriatric day hospital. *Clin Rehabil*. 2001; 15: 296-300.

43. Katz S, Downs TD, Cash HR and Grotz RC. Progress in development of the index of ADL. *Gerontologist*. 1970; 10: 20-30.

44. Voeten SC, Arends AJ, Wouters M, et al. The Dutch Hip Fracture Audit: evaluation of the quality of multidisciplinary hip fracture care in the Netherlands. *Arch Osteoporos*. 2019; 14: 28.

45. Fisher S, Ottenbacher KJ, Goodwin JS, Graham JE and Ostir GV. Short Physical Performance Battery in hospitalized older adults. *Aging Clin Exp Res*. 2009; 21: 445-52.

46. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*. 2000; 55: M221-31.

47. Oud FM, de Rooij SE, Schuurman T, Duijvelaar KM and van Munster BC. [Predictive value of the VMS theme 'Frail elderly': delirium, falling and mortality in elderly hospital patients]. *Ned Tijdschr Geneeskd*. 2015; 159: A8491.

48. Gavinski K, Carnahan R and Weckmann M. Validation of the delirium observation screening scale in a hospitalized older population. *J Hosp Med*. 2016; 11: 494-7.

49. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013; 22: 1717-27.

50. van der Sijp MPL, van Eijk M, Krijnen P, Schipper IB, Achterberg WP and Niggebrugge AHP. Screening for malnutrition in patients admitted to the hospital with a proximal femoral fracture. *Injury*. 2018; 49: 2239-43.

51. Rubenstein LZ, Harker JO, Salva A, Guigoz Y and Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci*. 2001; 56: M366-72.

52. Meetinstrumenten in de zorg, Hand-held dynamometer. Netherlands.

53. Tuijl JP, Scholte EM, de Craen AJ and van der Mast RC. Screening for cognitive impairment in older general hospital patients: comparison of the Six-Item Cognitive Impairment Test with the Mini-Mental State Examination. *Int J Geriatr Psychiatry*. 2012; 27: 755-62.

54. Parenti N, Reggiani ML, Percudani D and Melotti RM. Reliability of American Society of Anesthesiologists physical status classification. *Indian J Anaesth*. 2016; 60: 208-14.

55. Jorstad EC, Hauer K, Becker C, Lamb SE and ProFa NEG. Measuring the psychological outcomes of falling: a systematic review. *J Am Geriatr Soc*. 2005; 53: 501-10.

56. van der Sijp MPL, Schipper IB, Keizer SB, Krijnen P and Niggebrugge AHP. Prospective comparison of the anterior and lateral approach in hemiarthroplasty for hip fractures: a study protocol. *BMC Musculoskelet Disord*. 2017; 18: 361.

57. Soininen P, Kangas AJ, Wurtz P, Suna T and Ala-Korpela M. Quantitative serum nuclear magnetic resonance metabolomics in cardiovascular epidemiology and genetics. *Circ Cardiovasc Genet*. 2015; 8: 192-206.

58. Wurtz P, Kangas AJ, Soininen P, Lawlor DA, Davey Smith G and Ala-Korpela M. Quantitative Serum Nuclear Magnetic Resonance Metabolomics in Large-Scale Epidemiology: A Primer on -Omic Technologies. *Am J Epidemiol*. 2017; 186: 1084-96.

59. t Hart LM, Vogelzangs N, Mook-Kanamori DO, et al. Blood Metabolomic Measures Associate With Present and Future Glycemic Control in Type 2 Diabetes. *J Clin Endocrinol Metab*. 2018; 103: 4569-79.

60. Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49: 1373-9.

61. Harrell FE, Jr., Lee KL, Califf RM, Pryor DB and Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984; 3: 143-52.

62. Deelen J, Kettunen J, Fischer K, et al. A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. *Nat Commun*. 2019; 10: 3346.

63. Ouellet JA and Cooney LM, Jr. Hip Fracture: Can We Do Better? *J Am Geriatr Soc*. 2017; 65: 22-4.

64. Corcoles-Jimenez MP, Villada-Munera A, Del Egido-Fernandez MA, et al. Recovery of Activities of Daily Living Among Older People One Year After Hip Fracture. *Clinical Nursing Research*. 2015; 24: 604-23.

65. Chan DD, Tsou HH, Chang CB, et al. Integrated care for geriatric frailty and sarcopenia: a randomized control trial. *J Cachexia Sarcopenia Muscle*. 2017; 8: 78-88.