Research Protocol & Statistical Analysis Plan

Project Title:	"Risk Factors for Fall and Fracture – A Cohort Study of Fall-related Factors Obtained in Routine Orthopaedic Care"
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RISK FACTORS FOR FALL AND FRACTURE – A COHORT STUDY OF FALL RELATED FACTORS OBTAINED IN ROUTINE OTHOPAEDIC CARE

1. Introduction

The knowledge of risk factors for falls and fractures amongst older individuals are enormous, still identification of fallers and prevention of falls is not part of standard of care. Some risk factors are more or less overlooked, such as alcohol consumption, orthostatic reactions, as are increased risks related to common medications such as certain antidepressants, opioids and sedatives (1-3)

Functional activity and frailty scores have been suggested to be potential predictors of adverse events, length of hospital stay and mortality (4-6), but has not been implemented in routine care in Sweden.

Outcomes after fragility fractures are continuously poor, in particular well studied after hip fractures, although palpable improvements have been reached regarding surgical treatment. Are there other factors that are equally or more decisive for the global outcome from the patient's point of view?

2. Project aims

The overall aim of this project is to improve the global outcome for an ageing individual after a traumatic fall through promoting recovery and rehabilitation, and preventing complications, new falls and fractures. This will be addressed in the specific studies listed below, all of which will be based on an annual cohort of older individuals admitted due to a fall to the Department of Orthopedics, Malmö.

3. Planned studies

1. Risk factors associated with falls in an orthopaedic cohort – prevention possible?

Background: Risk factors associated with falls among the elderly have historically been well studied. However, the knowledge of risk factors for falls/fractures is mostly outdated, as those entering old age today have different health history, medications and lifestyle than the generations before them (7). Also, the routine health care is challenged by the growing the proportion of aged individuals in Sweden and the consequent increase in fall-related trauma and related conditions.

Many known risk factors, such as infection or orthostatic hypotension, arise from medically treatable conditions. However, mapping of factors contributing to fall is seldom done in routine healthcare, with the consequence that subsequent individualized fall prevention is obstructed (2).

Objective: This study aims to analyze results from a standardized set of blood tests, orthostatic test, hand grip test and scores for frailty and activity as explanatory variables for fall.

Material and Methods: An annual cohort of older individuals admitted due to a fall to the Department of Orthopedics, Malmö, will be screened with tests and scores. This data, together with basic demographics including +/– fracture, will be gathered in a RedCap-database.

Importance: Preventative measures can be tailored through early identification of individual risk factors. Also, early identification and treatment of simultaneous, feasibly severe, medical conditions might improve the morbidity and mortality of the frail elderly patient.

2. Association between factors identified at admission due to fall and 1-year clinical outcome

Background: See study 1.

Objective: Do risk factors identified at the time of the initial fall/fracture show an association with adverse events, re-admission, new fractures, or death? The study aims to analyze a standardized set of blood tests, orthostatic test, hand grip test and scores for frailty and activity as risk factors for an unfavorable outcome.

Material and Methods: Data from a 1-year-follow-up will be analyzed regarding readmission, new fractures and death.

Importance: See study 1.

3. Is calprotectin a more accurate predictor of bacterial infection than conventional testing?

Background: Bacterial infections (pneumonia, urinary tract infections, sepsis) are diagnostic challenges in the care of individuals suffering fall-related trauma. Infection as an underlying cause for falls is routinely assessed through clinical assessment and conventional blood work with C-Reactive Protein (CRP), white blood cell count (WBC) and body temperature at hospital admission. However, when a patient suffers a fracture, and in particular when surgically treated, the bodily response to trauma mimics the response to an infection, with elevated CRP and subfebrility (8-11). Meanwhile, geriatric patients frequently present with atypical signs of infection, such as confusion or absence of fever (12). As many aged individuals either have a concurrent infection as cause for their fall or early develop urinary tract infection or pneumonia, diagnostic difficulties occur.

Several biochemical markers have been suggested to be more sensitive and specific markers of infection. Elevated levels of CRP and procalcitonin (PCT), two common markers used in clinical settings, can be measures after 4 hours. PCT has been proposed to be a more sensitive marker for bacterial infection vs non-viral infection than CRP (13). However, it has been criticized for its non-specificity in differential diagnostics (14). Another marker, calprotectin, is released from neutrophiles at the time of activation in response to bacterial infection, and elevated levels can be measured within a few hours of activation. It has been proposed to be a more sensitive and a better prognostic marker in patients presenting with sepsis (11) and more sensitive in distinguishing bacterial respiratory infections (10) compared to PCT. However, the diagnostic value of calprotectin as an early infection marker in routine orthopaedic care has not yet been assessed.

Objective: To determine whether serum-calprotectin is a more specific test in the early stage of bacterial infection concurrent to a fracture, and if the test can improve the diagnostic accuracy.
Material & Methods: Individuals with hip fractures will be monitored with calprotectin as part of the routine blood test at admission and at 3rd day. Correlation between elevated calprotectin and other infection markers and any infection diagnosed by conventional means (culture, radiology etcetera) will be studied. Prognostic value of calprotectin, PCT vs CRP will be assessed.
Importance: Through early and correct diagnosis of infection, early treatment can be initiated and more severe conditions associated with high morbidity and mortality, such as sepsis, might be prevented. Objective and routine testing is particularly important in patients with cognitive impairment, who cannot communicate their symptoms.

4. Is harmful alcohol consumption an underrated cause of falls in the older population?

Background: Excess alcohol consumption might be an underestimated risk factor for fall among the elderly. During 2006–2021 in Sweden, an increase in self-reported hazardous alcohol consumption was found in age groups 45–64 and 65–84 years. For women >65 yrs, an increase from 3 to 8% was seen, and for men 9 to 14% (15). Phosphatidylethanol (PEth) is a measurable marker for alcohol consumption with high specificity and sensitivity. Accumulation of these phospholipid groups is seen through repeated alcohol intake which makes PEth a marker suitable for screening long-term (a few weeks) consumption. PEth is routinely analyzed in Swedish laboratories and is used as a routine blood test in psychiatric and cognitive

assessments. To our knowledge, the use of PEth in routine orthopaedic care to evaluate excess alcohol consumption has not been described in previous literature.

Objective: To describe the rate of harmful alcohol consumption in a cohort of individuals ≥65 years who need hospital treatment due to fall with or without fracture.

Material & Methods: By integrating phosphatidylethanol (PEth) into the routine blood tests taken after admittance, individuals with harmful consumption or substance use disorder can be better identified.

Importance: The readiness to identify and offer treatment for individuals with harmful alcohol consumption is low. In the acute trauma setting, untreated withdrawal symptoms can impact both somatic and psychological function.

5. How to best depict the functional capacity of an older individual in need of treatment and rehabilitation after a fall?

Background: Both the immediate treatment after a fall and the rehabilitation plan are guided by the functional demands and physical capacity of the patient. This is often left to plain "eyeballing" based on clinical experience. Such subjective methods can lead to unequal provision of healthcare (16).

Objective: To compare the concordance between simple methods to evaluate the physical and functional capacity of an individual over 60 years of age.

Material & Methods: By scoring of frailty and activity aided by validated score systems, and by measuring hand grip strength, the capacity of the individual will be depicted in different aspects. Both the concordance of the measurements, and the association of each with 30-day- and 1-year-mortality will be studied.

Importance: To our knowledge, the value of using these validated instruments in clinical orthopaedic care has not been studied previously. With the help of these instruments, the frailest individuals might be identified in-patient and tailored further support may be provided.

6. What are the differences between those with fall only or fall leading to fracture?

Background: The prognosis and management after a hip fracture is well described in the literature, but little is known about the clinical outcome of individuals who "only" fall without a fracture (17). Furthermore, there are no standardized follow-up- or rehabilitation schedules up to date.

Objective: To compare the baseline characteristics during hospitalization and clinical outcome (adverse events, re-admission, new fractures or death) of individuals over 60 years of age who fall without vs with a fracture.

Material & Methods: By using the standardized blood tests, frailty and activity scores measuring hand grip strength after a fall, possible baseline differences between individuals who need hospital care due to a fall without versus with a fracture will be detected. Adverse events, re-admission, new fractures or death in the two groups will be analyzed during the 1st year after the fall.

Importance: Through knowledge of the outcome after a "simple" fall without a fracture, further standardized care models can be established.

7. Is shrunken pore syndrome associated with 1-year mortality and frailty in patients after a fall?

Baackground: SPS is a selective filtration defect of the kidneys, which has previously been associated with mortality and cardiovascular diseases in selected cohorts (18, 19). SPS was first described in 2015, hence, questions regarding prevalence, stability over time and association with adverse outcomes remains to be answered.

Objective: To determine if shrunken pore syndrome (SPS) is associated with frailty and 1-year mortality in older patients admitted to Skåne university hospital after a fall.

Material & Methods: Estimated glomerular filtration rate (eGFR) will be assessed in each individual based on creatinine and cystatin C. SPS will be defined as an eGFRcysC/eGFRcrea ratio < 0.6. Association between SPS, frailty and 1-year mortality will be assessed in the cohort described above.

Importance: Given the novelty of SPS, studies investigating this syndrome is frontline research.

8. Is there a correlation between pro-BNP and orthostatic hypotension and 1-year outcome after a fall?

Background: Orthostatic hypotension is a known risk factor for falls and fractures (20). Pro-BNP is a marker for diagnosing and monitoring congestive heart failure. These clinically readily available tests have not been routinely used in orthopaedic care in Sweden, although the orthogeriatric cohort represents with multiple comorbidities including cardiovascular dysfunction.

Objective: To study the correlation between pro-BNP and the results from orthostatic tests and to describe the prevalence of orthostatic hypotension (symptomatic versus asymptomatic) and to study the association between biomarkers, blood pressure and 1-year fracture rate and mortality in patients admitted to Skåne university hospital for falls and fractures.

Material & Methods: Pro-BNP will be assessed in each individual and a modified orthostatic test will be performed. Association between biomarkers, blood pressure and 1-year fracture rate and mortality will be assessed.

Importance: Further research is needed to determine the value of cardiovascular markers and orthostatic tests in clinical settings. Through identification and treatment of orthostatic hypotension and congestive heart disease during hospital stay, improvements in the short- and long-term outcome might be done.

4. Study design

This is a longitudinal observational cohort study. Study inclusion period starts in February 1st 2023 and ends 365 days after the study started. Each individual is followed up for 1 year, calculated from the date of admission to in-patient ward.

Inclusion & Exclusion Criteria

Individuals aged 65 years or older at the time of admission to Department of Orthopaedics at Skåne University Hospital in Malmö, Sweden, due to a fall-related trauma will be available for inclusion.

Only individuals for whom the standard clinical pathway is followed are included. This means that individuals who are treated at any other department (including ICU) prior to their care at the Department of Orthopaedics are excluded. Those transferred from other hospitals for further care are also excluded. Those who suffer trauma through high-energy injury are included but may be separately analyzed.

Cognitive impairment or other native tongue language are not reasons for exclusion as no active participant contribution is requested.

5. Covariates

Baseline demographic characteristics and clinical measurements are expected to have an influence on primary and secondary outcomes, to different degrees. Depending on the specific objective in each study described in the study protocol, these data are to be used 1) as covariates for risk analyses, 2) for subgrouping individuals, and 3) to adjust for confounders in survival analyses.

Type of data collected

1. **Demographics**
   Age/Date of birth
   Sex
2. **Circumstances**
   Date of fall, admission & discharge
   Living alone versus not (including assisted living facilities)
   Alcohol (current/previous/no known or suspected excess use)
   Smoking (yes/previous/no)
   Oral health (good/poor/unknown)
   Immobilization >24 h prior to admission (yes/no)
   Readmission (yes/no)
3. **Injury characteristics**
   Type of injury (no fracture/fracture type)
   Treatment (surgical versus non-surgical, primary vs reoperation)
   Date of surgery
   Type of surgery/reoperation (internal fixation/arthroplasty/revision surgery or amputation due to infection/other)
4. **Comorbidities**
   Chronic illnesses or past conditions with sequele (e.g. stroke) before admission versus acute conditions are separately assessed through medical records, including the following diagnoses according to ICD-codes: C00-C97, C79.5, D50-64, E00-E07, E10.4, E11.4, E10-E14, E20-E21, E86.9, F00-F09, G30-G32, F10-F19, F30-F39, G20-G26, G40-G41, G60-G64, G80-G83, H53-H54, I20-I25, I48, I50, I60-I64, I95.1, J40-J47, K70-K77, M05-M14, M80-M85, N17-N19, R41, R42
   In case of hip fracture, following comorbidities are further specified: B20-B24, C81-C96, D80-D84, E10.6D+E11.6D, L89, L97, R13, I70-I79, E10.5+E11.5
   In case of hip fracture: ASA grade from the anesthesiologist's preoperative assessment.
5. **Medication**
   Medicines before admission are assessed ("at home" -medication) and are classified according to ATC-groups, and including the following: A02BC, A10A, A10B, B01A, C03A-C, C03D-E, C07, C08-C09, G03XC, H02AB, H03A, H03B, H05A, L01+L04, L02AE, L02BA, L02BG, M01A, M03B, M05B, N02A, N03A, N04B, N05A, N05BA+N05CD, N05CF, N06AA+N06AF-G, N06AB, N06AX, R06AD+N05BB+N05CM, N06D
6. **Physical assessments during hospital stay**
   Body Mass Index (weight/height^2)
   Body temperature (twice daily, tympanic measurement)
   Hand grip strength (dominant or uninjured hand, best out of three measurements)
   Orthostatic test (a drop of ≥ 20 mmHg in the systolic blood pressure or a drop of ≥ 10 mmHg in diastolic blood pressure are considered significant results, and orthostatic symptoms within 3 minutes of standing are noted)
7. **Scoring of frailty/activity**
   Clinical Frailty Score (1-9 p, status before fall)
   Frändin-Grimby scale (1-6 p, status before fall)
   Cumulative Ambulation Score (0-6 p, status before fall, daily current status)
   ASA-score (1-5 p, before surgery)
8. **Blood samples**
   Taken at the time of admission: Albumin, ESR, CRP, WBC with differential count, Ca-ion, vitamin D, ALP, TSH, T4, PTH, PEth (hip fracture patients only), estimated eGFR, cystatin C, creatinine, potassium, sodium, B12, folate, glucose, pro-BNP (fracture patients only), calprotectin (hip fracture patients only), procalcitonin (hip fracture patients only)
   Taken on the 3rd day of admission/post-surgery: Hb, creatinine, potassium, sodium, CRP, WBC, calprotectin (hip fracture patients only), procalcitonin (hip fracture patients only)

9. **Surgical factors for hip fractures**
   Surgery time (from knife start to end, min)
   Surgical method (internal fixation vs arthroplasty)
   Waiting time (from diagnostic X-ray to knife start, hours).
10. **Local surgical complications** (early=0-30 days vs late=30-365 days, from date of admission)
    Surgical site infection
    Other surgical wound complication (bleeding/hematoma/increased discharge)
    Implant failure
    Reoperation (reason, type)
11. **Medical complications** (early, 0-30 days vs late, 31-365 days, from date of admission)
    Medical complications are assessed at the time of admission, during in-patient care (pre-/post-surgery) and after discharge from hospital, and include the following:
    UTI, pneumonia (radiological verification – yes/no), DVT (ultrasound verification – yes/no), LE (CT-scan verification – yes/no), confusion/delirium (through medical records), acute coronary syndrom (unstable angina, STEMI, NSTEMI), acute kidney failure (laboratory tests), pre- and post-surgical anaemia (Hb<100 post-surgery), stroke/intracranial hemorrhage (radiological verification), atrial fibrillation (ECG), sepsis (defined by Sepsis3).
12. **Readmission**
    Date of readmission
    Reason of readmission
13. **Other complications**
    New fall
    New fracture
    Death (date of death)

Control groups for baseline data:
- Blood samples = predefined pathological norm values according to local laboratory
- Hand grip strength classified as weak / normal / strong according to norm values
- Alcohol consumption: Data based on reading of medical journals exist from an annual cohort of older patients with hip fracture in Malmö 2011. Alcohol use measured by the AUDIT questionnaire was obtained from a Malmö cohort of 57 hip fracture patients aged 20 to 60 years. Self-reported alcohol consumption is available from a Swedish national sample divided in age groups.

6. Outcome measures

The outcome measures differ between the substudies. The primary outcomes in each substudy are the following

1. Prevention: Prevalence of risk factors associated with falls in an orthopaedic cohort.

2. Predictors: Association between risk factors identified at admission due to fall and clinical outcome within 1 year (complications, readmission, new falls, death)

3. Infection: Correlation between elevated calprotectin and any infection diagnosed conventionally (culture, radiology, etc.) within 1 month. The performance of calprotectin as markers for bacterial infection and 1-month mortality compared to procalcitonin, C-reactive protein, ESR, leukocytes and temperature. Clinical course during 1 year post-fracture, regarding death, readmission, new cases/fractures and adverse events – group comparisons between those who develop early infection and those who do not.

4. Alcohol: Prevalence of harmful alcohol consumption in association with a fall injury. Association between such and 1-month (confusion, infection) and 1-year complications.

5. Renal disease: Prevalence of shrunken pore syndrome in association with a fall injury. Association between such and 1-month (acute renal failure) and 1-year complications.

6. Scores for frailty and activity: Correlation between the different instruments and 1-month and 1-year mortality.

7. Study groups

The study participants will be grouped depending on the specific objectives of each planned study.

Planned study groups are the following:

1) All individuals included regardless of presence or absence of fracture
    a. Study 1, 2 & 5: All individuals, no group comparison.
    b. Study 6: Subanalysis of individuals who fall without vs with a fracture (with subsets according to type of fracture)
    c. Study 7: Subanalysis of individuals with shrunken pore syndrome vs no shrunken pore syndrome.
    d. Study 8: Subanalysis of individuals with elevated proBNP or orthostatic hypotension vs with "normal" parameters.
2) Individuals who obtained a fracture
    a. Study 4: Comparison with historical records of estimated alcohol consumption. Subanalysis of individuals with low alcohol comsumption (pETh <0,05 μ/L), intermediate consumption 0,05–0,3 μ/L) and high consumption (>0,3 μ/L).
3) Individuals who obtained a hip fracture
    a. Study 3. Subanalysis of individuals with with or without elevated calprotectin.

8. Study Assessments (Timing)

The following measurements will be assessed within a 1-year study period, starting February 1st, 2023:

Frailty: Classification based on the Clinical Frailty Score (CFS) (21). *Activity*: Classifications based on Frändin-Grimby scale (22) and Cumulative Ambulation Score (CAS) (23). *Blood samples*: Albumin, CRP, WBC with differential count, ESR, Ca-ion, vitamine D, ALP, TSH, T4, PTH, PEth, pro-BNP, eGFR, cystatin C, creatinine, potassium, sodium, B12, folate, glucose, procalcitonin and calprotectin. *Temperature*: Taken twice daily. *Orthostatic test:* Up until max 3 minutes only. *Hand grip strength*: Best hand (dominate or the uninjured side, in case of arm injury) (24). *BMI*: Weight/(height)^2.

Scheme	At Admission to Dept of Ort.	Day 1 as In-patient	Days 3-4 as In-patient	Day 5 as In-patient – Discharge from Ward
Blood samples	X		X[2]	
Temperature	X	X	X	X
Grip Strength Test[1]			X	X
Orthostatic Test[1]			X	X
Questionnaires[1] (CFS, Activity Score, CAS)		X	X	X
Weight/height			X	

Table 1: Schedule for routine testing.
Explanations: X=Recommended timing..

[1]To be assessed only once at any timing. Orthostatic test is only assessed in individuals with injury in upper extremities only.
[2]Calprotectin and procalcitonin are to be taken on 1st and 3rd day of admission/or post-surgery, together with other standardized "3rd day-tests".

9. Time Plan

2022 – autumn:	Practical preparations at the wards
2023 – entire year:	Inclusion
2024 – entire year:	Follow-up period. Analysis of baseline data. Manuscript writing.
2025 – spring:	Analysis of 1-year data.
2025 – autumn:	Manuscript writing, 1-year data.

10. Missing Data

Due to the nature of acute trauma care, we expect that not all individuals receive all the planned assessments described in Section 3. The extent of missing data will be quantified and presented. Possible selection bias due to missing data will be addressed by identification of the cause, when available. The results might be biased e.g. due to early discharge or death, missing patient co-operation due to confusion or dementia. Therefore, individuals are not excluded from analyses due to missing data as a fundamental rule.

11. Statistical Methods

Descriptive Statistics

Descriptive statistics will mainly be presented in table format, in means (± standard deviations), medians (range) and in proportions (%) depending on the type of data.

Inferential Statistics

Statistical methods will vary between studies, depending on the specific objectives. T-test and ANOVA, and their alternative non-parametric methods for continuous parameters and Chi-square or Z test for proportions will be used to compare characteristics between two or more groups. Different regression models, depending on the specific objective, will be applied to assess predictors of outcome measures. Survival analyses might be adjusted for confounders, such as significant differences between studied groups in age or gender at the baseline. Competing risk models are to be applied in substudies with longitudinal design, where mortality is expected to be a competing risk.

Statistical Significance

A p-value <0.05 is considered statistically significant. Decreasing statistical strength through smaller sample sizes will be taken into consideration when discussing the results.

12. Importance and novelty

In general, a new generation is suffering frailty, falls and injuries coupled to ageing. We need to explore if people born in the 1940's enter this phase in life due to the same reasons as previous generations, and if they meet the same severe consequences of such injuries. Updated knowledge is needed to tailor further treatment and preventive measures, thus meeting the need of health care today and in the future. Also, using updated methods and technology will improve care and outcome. Better diagnostic tools for infection, renal disease and orthostatism can speed up correct diagnosis and specific treatment.

The quality of the care, treatment and rehabilitation given depends on a proper understanding of the person in front of you. Understanding that the person escaping a fall without a fracture may have the same pessimistic outcome as the one who suffer a fracture, or that hazardous alcohol consumption is a reality

also in the oldest, will affect how we provide a better care in the future. Likewise, more objective methods of evaluate physical capacity to design a valid rehabilitation plan will have clinical importance.

13. Collaborations

Skane University Hospital:
Cecilia Rogmark – principal investigator. MD, PhD, ass. prof. Orthopaedic surgeon.
Linnea Malmgren – MD, PhD. Geriatrician.
Helmi-Sisko Pyrhönen – PhD student, MD. Junior physician.
Viktor Hamrefors – MD, PhD, ass. prof. Cardiologist.

Lund University:
Eva Ekvall-Hansson – PT, PhD, prof. Physioth.

Karolinska Institute:
Åsa Magnusson – MD, PhD, lecturer. Specialist in addictive medicine.

Additional researchers are to be recruited, including PhD students, and a physiotherapist.

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