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Prognostics of recovery in hip fracture patients

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Chapter 1

General introduction

Epidemiology

Proximal femoral fractures are amongst the most prevalent fractures in older patients. The lifetime risk for women in Western countries is about 12%, and 5% for men.[1] In the Netherlands, the combined incidence of approximately 20.000 proximal femoral fractures annually accounts for about 500 million euro's in acute treatment costs, which corresponds with 0.5% of the total national healthcare budget.[2-4]

The high risk for this type of fracture results from a variety of age-related health factors. The average patient is aged 80 years or older and has significant comorbidities.[2] Up to 40% of patients already experienced onsets of disability shortly before the fracture.[5] The typical trauma mechanism is a fall from a standing height on the ipsilateral hip.[6] The risk of falling increases with age, and simple falls are the leading cause of traumatic injury and death in patients 65 years of age and older.[7, 8] The age-related factors contributing to a fall include musculoskeletal disorders (impaired strength due to sarcopenia, joint pain associated with arthritis or degenerative arthropathies), cardiovascular disorders (temporary loss of consciousness due to cardiac arrythmias, orthostatic hypotension, myocardial infarction), neurological disorders (impaired functionality due to stroke, Parkinsonism or diabetic neuropathy), impaired vision, medication induced vertigo, hypoglycaemia and infections.[8] In most cases, a specific cause is hard to determine, as it is often a combination of multiple factors.

Etiopathogenesis

Although the femur is the largest and strongest long bone, the bone quality can be so poor in older people, that a low-energy trauma results in a fracture.[9] The poor bone quality is characterized by a low bone mass density: the definition of osteoporosis.[10-12] In older women, osteoporosis is most frequently attributed to a postmenopausal hormonal disbalance which leads to a systemic increase in the reabsorption and insufficient mineralization of bone.[10] Consequently, these fractures are more than twice as prevalent in women compared to men.[13] Diminished physical activity, chronic disease, poor calcium and vitamin D intake and medication can also lead to severe osteoporosis at an old age in both sexes.[14]

Fractures caused by these age-related factors are collectively referred to as 'fragility fractures'.[15, 16] Besides the proximal femur, which accounts for approximately 18% of these fractures, other common fractures are of the distal radius, vertebrae, proximal humerus and pelvis.[13] The social and economic impact of most other fragility fractures, however, is by far not as significant as that of the proximal femoral fractures.[17] Fragility fractures other than the proximal femur are often treated conservatively, and cause less morbidity and functional impairment.

Treatment

Proximal femoral fractures are often extremely painful as they cover a large area of bone and periosteum.[18, 19] In addition, muscle tension of the upper extremity causes rotation and compression at the fracture site. Bearing weight on the fractured extremity is extremely painful, unstable and risks an increase in the displacement in virtually all types of fractures except the stable fractures.[20, 21] Closed anatomic reduction and fixation with a splint to effectively stabilize the fracture and enable mobility is practically impossible.[22]

In general, the primary aim of proximal femoral fracture surgery is to allow for immediate mobilization and early rehabilitation. In contrast to many other long bone fractures treated surgically with internal fixation, successful fixation of a proximal femoral fracture allows for relatively immediate and unrestricted activity. Alternatively, replacement of the fracture by prosthesis implantation removes the fracture site altogether and allows for immediate mobilization also.

The surgical options (osteosynthesis or prosthesis) are determined by the anatomical fracture characteristics, the patient's condition and the patient's prefracture mobility. The two main groups of proximal femoral fractures, femoral neck fractures and pertrochanteric fractures, each pose their own therapeutic challenges.[23] Femoral neck fractures are located in the collum femoris, between the femoral head and the trochanter complex.[24] Displacement in this type of fracture can lead to a disruption of the blood-supply to the femoral head, which is provided by femoral circumflex arteries running around the femoral neck.[24] This can lead to an avascular osteonecrosis of the femoral head or non-union of the fracture. For this reason displaced fractures are frequently treated with arthroplasty, especially in older patients with limited mobility.[25-27] The operation requires an approach to the hip joint that provides an adequate exposure to remove the femoral head and insert a prosthesis in the femoral canal. The approach can be performed in a number of ways, but all require substantial traumatic manipulation of the surrounding tissues, which may affect outcomes in different ways. Trochanteric fractures intersect either the major trochanter or the lesser trochanter of the femur, and are often comminuted.[28] These fractures pose little risk for avascular necrosis and the main goal of the surgical procedure is to achieve an adequate fracture stability.[29] Fixation with intramedullary nails tend to provide the most stability with the best outcomes.[30-32]

Practice to regain mobility starts as early as possible after surgery.[33, 34] During admission patients are instructed by a physiotherapist and train mobility, including transfers in and out of bed, use of walking aids, walking short indoor distances and climbing stairs.

Patients who previously lived in a nursing home can frequently return to the same institution and receive locally organized rehabilitation and upscaling of professional care if necessary. In the Netherlands, these nursing home patients are not eligible for rehabilitation conform the geriatric rehabilitation DBC, but for another, more limited care package (ZZP9B). The majority of patients, however, lived independently at home without personal care before occurrence of the fracture.[35] Generally, the more fit patients are mobilized sufficiently during the hospital admission to be able to make independent transfers, walk indoors and go to the bathroom. This is considered self-reliant enough to return safely to their independent living situation, if necessary with the aid of caregivers or professional home-care.[36] Further rehabilitation through physiotherapy can be provided by home visits of the physiotherapist or in an ambulatory setting.[37] This applies to approximately 40-50% of the prefracture community dwelling patients.[38, 39] For those patients who have not recovered sufficiently during admission, or for those patients whose premorbid home-situation proves problematic due to logistic or organizational reasons, temporary admission to a specialized rehabilitation home for geriatric rehabilitation is warranted. This option has gained favour in the past decades.[40]

Currently, limited consensus and no validated rehabilitation protocols designed specifically for patients with a proximal femoral fracture exists in the Netherlands and elsewhere.[41] Although many studies on more elaborate rehabilitation programs have indicated improved outcomes, few are validated and no single evidence-based program is advised.[42, 43]

Outcomes

Proximal femoral fractures can have a detrimental impact on patients, including mortality, disability, loss of independence, depression and fear of falling.[44, 45] Despite the high standards of in-hospital care and the availability of rehabilitation options in developed countries, the survival remains poor.[46] In-hospital mortality rates are about 3% and rises to about 20% at one-year after treatment.[47-50] Large studies on survival revealed a significant excess mortality in this population, indicating an elevated mortality risk inherent to the fracture and treatment itself.[49, 50] This implies a big potential for improvements. But despite many efforts, little progress has been made in contrasts with other conditions such as heart disease, stroke, and cancer, for which significant improvement in survival has been achieved over the past decades.[46, 51]

Much of the morbidity in patients with a proximal femoral fracture is caused by perioperative complications. Complication rates of up to 75% have been described in literature, of which the majority are non-surgical, such as delirium, pneumoniae, urinary tract infections, pressure-sores and heart failure.[52] Many of the risk factors associated with these complications are age related. Improvements in the perioperative management, more specifically in geriatric management, may help to deter the onset of these complications.[52]

In addition, significant adversity is caused by deterioration of the patient's functionality. Older adults are expected to experience a gradual loss of function over time, but acute injury has a sudden effect from which at least half of all proximal femoral fracture patients do not fully recover.[44, 53, 54] One-third of all prefracture community dwelling patients are permanently institutionalized due to subsequent loss of independence.[38] This loss of self-reliance goes hand in hand with a loss in privacy and health-care costs associated with homecare requirements or admissions to nursing homes.

Although surgical complications after proximal femoral fractures are relatively rare compared to non-surgical complications, the consequences are often severe. Osteosynthesis can result in fracture-healing complications that generally require revision surgery.[55] This should be taken into consideration when the use of osteosyntheses rather than hip arthroplasty for femoral neck fractures in older patients is considered.[56-58] Arthroplasty, however, poses its own risks including dislocation of the prosthesis, periprosthetic fracture and deep wound infection.[55] The forementioned surgical complications often lead to readmissions, reoperations and prolonged patient immobilization. This could cause delays in the patients' rehabilitation, but the effects of surgical complications on functional outcome are poorly studied.[59, 60] Despite many improvements in the surgical techniques over the past decades, very little effect has been observed for the patient outcomes.[46]

Due to the unimproved outcomes and prevalence of complex medical and social needs, the treatment goal has shifted away from merely fracture treatment to a more holistic approach aimed at optimal recovery.[61] In recent decades, this has led to the development of ortho-geriatric care units, where older patients are treated by a multidisciplinary team including a geriatrician. This is aimed at mapping and addressing frailty characteristics in order to optimise recovery strategies. The holistic approach can include assessments of cognition, nutritional status, comorbidities and depression, which have all been associated with outcomes.[62] Malnutrition has a high prevalence in this patient population and adequate treatment with diets and supplements has shown positive effects on complication rates, mortality and quality of life.[63-66] Formal falls assessments are another method of secondary prevention and have been shown to reduce morbidity through the management of the aforementioned risk factors.[67] The fear of falling, which has a prevalence of over 50% in these patients, can impair mobility through avoidance.[68] Different interventions developed to mitigate the fear of falling, however, have shown inconsistent outcomes.[69-71]

Overall, the collaborative care models with geriatricians for patients with a proximal femoral fracture have shown improvements in outcomes, including mortality rates and mobility.[72-75] Currently, orthogeriatric management is provided for 78% of the operated patients aged 70 years and older in the Netherlands, but only 23% is treated in a special comprehensive orthogeriatric ward.[2]

Prognostics

Prognostication is a fundamental clinical activity and an important concern for patients and physicians.[76-78] Both need prognostic information to determine treatment strategies and anticipate advance care planning.[76] Exploring ways to improve patient care requires sufficient knowledge on the relevant factors. Modifiable factors, such as nutritional state, anaemia and management of comorbidities may be targets for interventions while unmodifiable factors such as functional and cognitive impairments may be valuable for the prognostic accuracy and advanced care planning.[79] The prognostic accuracy of functional recovery is vital for a variety of decisions during the treatment process. It could be used to determine whether patients are more eligible for femoral head reduction surgery or total hip arthroplasty, whether they would benefit from more, less, or different types of physiotherapy and training, or whether care in the patients living situation should be temporarily or permanently upscaled.

Numerous prognostic factors of functional recovery have been studied.[79] From these, prediction models have been constructed and studied in relation to adverse outcomes (predominantly mortality).[80, 81] The prefracture status of patients, including function and comorbidities such as those mentioned before, seems most relevant for the functional recovery. The enormous heterogeneity in the health status of older patients, however, makes for poor prognostic accuracies of the current studied models.[79] This may in part be explained by the limited understanding of the complex underlying mechanisms and mediators.[79]

Aim and outline of this thesis

The primary aim of this thesis is to provide a better understanding of the factors relevant for survival and the functional prognosis of patients with a proximal femoral fracture. The thesis is divided into two parts.

Part I focusses on the surgical approaches for arthroplasty in patients with a proximal femoral fracture. *Chapter 2* provides an overview of the available literature on the main surgical approaches. A meta-analysis was performed to compare surgical outcomes, complication rates, survival and the functional outcomes of each approach. *Chapter 3* describes the current application of the anterior and lateral approach in clinical practice and its surgical outcomes in a prospective observational cohort study.

Part II focusses on the methods to assess prognostic factors and their independent relevance for functional outcomes. Factors including the nutritional status, general health status, cognition and serum metabolites are studied to create a better understating of a patient's physical capacity for rehabilitation. Methods to assess the nutritional state of an older proximal femoral fracture patient during admission are discussed in *Chapter 4*. An overview of the available literature on independent prognostic factors of long-term functional outcome is provided in *Chapter 5*. *Chapter 6* to *8* elaborate on a new way to define functional outcome using a composite outcome. In *Chapter 6*, this outcome is used to study prognostic factors for resilient patients using a multi-state model. *Chapter 7* describes a design article for a prospective study focused on the effects of muscle strength and sarcopenia. The relevance of serum metabolites, which have been used to define a mortality risk score, is explored in *Chapter 8*.

The main findings of this thesis and their implications are discussed in a broader context in the General Discussion (*Chapter 9*). Future perspectives on the treatment of patients with a proximal femoral fracture and the field of prognostic research in particular are also discussed in this chapter.

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Part I

The anterior approach for arthroplasty

Chapter 2

Surgical approaches for hemiarthroplasty: a meta-analysis

van der Sijp M.P.L., van Delft D., Krijnen P., Niggebrugge A.H.P., Schipper I.B. Surgical Approaches and Hemiarthroplasty Outcomes for Femoral Neck Fractures: A Meta-Analysis. *J Arthroplasty. 2018 May;33(5):1617-1627.e9. Corrigendum. J Arthroplasty. 2019 Nov; pii: S0883-5403(19)31029-0.*

Abstract

Background: The lateral approach (LA), posterior approach (PA), and anterior approach (AA) are conventional surgical access routes for hemiarthroplasty in proximal femoral fractures. This meta-analysis assesses and compares the outcomes and attempts to identify the best approach for hemiarthroplasty in the treatment of proximal femoral fractures.

Methods: An electronic search was performed from inception to October 25, 2017, for comparative studies including at least 2 of the conventional approaches. Outcomes including operation time, surgical blood loss, perioperative fractures, wound infections, dislocations, and hospital length of stay were plotted in forest plots.

Results: Twenty-one eligible studies were selected including 3 randomized, controlled trials, 7 prospective and 11 retrospective cohort studies. The odds ratio (OR) for dislocations was significantly higher for the PA compared with the AA (OR, 2.61; 95% confidence interval [CI], 1.26 to 5.43; $P = .01$) and the LA (OR, 2.90; 95% CI, 1.63 to 5.14; $P = .0003$). The PA had a higher risk of reoperation compared to the AA (OR, 1.25; 95% CI, 1.12 to 1.41; $P < .0001$). No significant differences were found concerning perioperative fractures, wound infections, and hospital length of stay. Some studies suggest a better short-term functional outcome using the AA compared to the PA.

Conclusion: The PA for hemiarthroplasty in proximal femoral fractures poses an increased risk of dislocation and reoperation compared to the LA and AA. There are no evident advantages of the PA and its routine use for fracture-related hemiarthroplasty should be questioned.

Introduction

The proximal femoral fracture is one of the commonest fractures in the older population, with a remaining lifetime risk of more than 10% in men and 20% in women over the age of 50.[1] Femoral neck fractures constitute more than half of these fractures, with displacement of the femoral head fragment in nearly 70%.[2] The displacement of the femoral head is associated with an increased risk of femoral head necrosis due to a disrupted blood flow at the femoral neck, delayed or nonunion and failure of internal fixation devices.[3] For this reason, displaced femoral neck fractures in older patients are often treated with hemiarthroplasty.[3] Replacement of the femoral head and neck with a hemiarthroplasty enables early mobilization which is desirable in older patients as prolonged rehabilitation is associated with high morbidity and mortality rates and increased healthcare costs.[3-5] The surgical approach used for hemiarthroplasty is expected to affect the treatment outcomes. Outcome differences have been described for complications such as dislocations, performance in daily activities and quality of life after the procedure, and the learning curve for surgeons.[6-11]

Three conventional approaches for hemiarthroplasty have been described since the 20th century with only slight modifications over time.[12-17] The lateral approach (LA) includes the lateral, direct lateral, straight lateral, omega lateral, Hardinge, Gammer, the McFarland and Osborne, transgluteal or transtrochanteric approach, and the anterolateral approach, also known as the Watson-Jones procedure.[18, 19] The LA requires (partial) separation and/or retraction of the insertion of the gluteus medius muscle for an adequate exposure of the capsule. In this approach, the distal aponeurotic insertion may be bisected, or a longitudinally trochanteric osteotomy may be performed.[19-21] In variations of the LA, the fibers of the gluteus medius muscle may be split with or without preservation of the vastogluteal continuity. In the anterolateral approach, an intermuscular plane is attained by anterior retraction or longitudinal division of the tensor fascia latae and posterior retraction of the gluteus medius muscle.[9, 22]

The posterior approach (PA) includes the true posterior approach, the posterolateral, back, dorsal, Moore and Southern approaches. It involves a longitudinal division of the gluteus maximus muscle along the fibers with detachment of the short external rotators, with or without preservation of the piriformis tendon for an adequate exposure of the hip joint.[20, 21, 23, 24]

The anterior approach (AA) includes the direct anterior or the true anterior, the Smith-Petersen, the anterior supine intermuscular, and the anterior minimal invasive surgery.[25] The AA uses the intermuscular plane between the sartorius, rectus femoris, and tensor fasciae latae for an adequate exposure of the anterior capsule.[23, 26]

Although outcomes of these approaches have been compared in numerous studies, none of the approaches has been identified as superior. The choice of a specific approach often seems solely to depend on the personal experience and preference of the surgeon, instead of evidence-based guidelines or protocols.[26, 27] Most surgeons are trained predominantly in one specific approach. The aim of this meta-analysis is to summarize the data of recent comparative studies on the outcomes of the 3 commonly used surgical approaches for hemiarthroplasty in the treatment of proximal femoral fractures, in an attempt to identify the preferable approach for treatment of displaced femoral neck fracture in the older patient.

Material and methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[28] No study protocol was published before the electronic search was conducted.

Search strategy

An electronic search was performed in PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews for studies comparing at least 2 of the conventional approaches (LA, PA, AA) up to October 25, 2017. Studies reporting outcomes of a single approach were deemed to be of insufficient comparative nature and unfit for this review. The electronic search strategy was developed in collaboration with an experienced medical librarian and edited for each specific electronic database. The search included exploded MeSH terms and keywords for hip fracture patients treated with hemiarthroplasty. The exact search strategy is presented in Appendix A.

Study selection

Two reviewers independently screened the titles and abstracts of all identified articles for eligibility using the "Covidence systematic review software" (Veritas Health Innovation, Melbourne, Australia). The full-text articles of the potentially relevant studies were read and eligibility for our review's purposes was agreed upon by the 2 reviewers. Any disagreements in the study selection process were resolved through discussion, if necessary with a third reviewer, until consensus was reached. The reference lists of all selected studies were screened for additional relevant citations that were not identified in the electronic search.

We included all randomized and observational studies reporting at least on 1 quantifiable outcome measure of at least 2 of the 3 approaches (LA, PA, AA) for hemiarthroplasty in hip fracture patients. All studies with one or more of the following characteristics were excluded:

- Studies published before 2000, to reflect the current state-of-the-art surgical instruments, materials and methods (other than the approach), healthcare guidelines, and rehabilitation.
- Studies without original data such as reviews and studies reporting on the same dataset without original or relevant results, in which case the most applicable study was included.
- Meeting abstracts, case reports, or studies including fewer than 20 patients.
- Studies on patients with predominantly nontraumatic indications for surgery such as arthrosis.

- Studies on patient groups with a specific comorbidity only.
- Studies including total hip arthroplasty and resurfacing surgery, as these procedures require different prostheses and surgical exposure of the hip.
- Studies on cadavers.
- Studies published and only available in languages other than English.

Data extraction

Data from the selected studies were extracted independently by the 2 reviewers. The study characteristics included the first author, year of publication, country, study design; the number, age, and sex of included patients per surgical approach, and duration of patient follow-up. Outcome measures included the operation time, surgical blood loss, hospital length of stay, incidence of perioperative fractures, wound infections, dislocations, reoperations, postoperative pain, functionality, and quality of life. Extracted raw data of the treatment outcomes can be found in Appendix B. Reported data were used to calculate percentages, incidences, and cumulative means. When incidence numbers were not reported, it was derived and calculated from the article data (such as incidence percentages) when possible. Outcome data reported as median value and range were converted to an estimated mean and standard deviation using the method described by Hozo et al.[29] Differences in the extracted data by the 2 reviewers were resolved by discussion.

Quality assessment

The methodological quality of the selected studies was independently assessed by the 2 reviewers. The 5-item revised tool for Risk of Bias in randomized trials (RoB 2.0)was used to score the risk of bias for all randomized, controlled trials (RCTs).[30, 31] Each item was scored using a 3-point scale corresponding with low risk of bias, some concerns about bias and high risk of bias in domains of the study design, and reported outcomes.

For nonrandomized studies, the 7-item Risk Of Bias in Nonrandomized Studies - of Interventions (ROBINS-I) tool was used.[32] A bias risk score (corresponding with low risk, moderate risk, serious risk, or critical risk of bias, or no available information) was assigned for domains of bias in the preintervention, at-intervention, and postintervention phase of the study.[32]

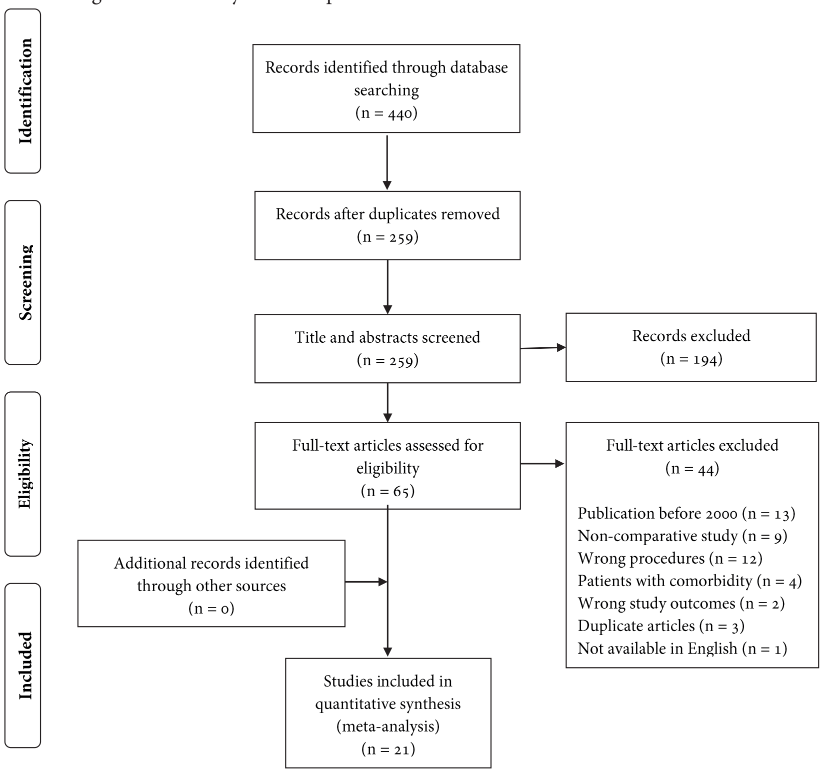
Statistical analysis

Outcome data were pooled if the study population and outcome definitions were similar. Meta-analysis was performed in Review Manager (RevMan) version 5.3 using a random effects model. To confirm the results, the meta-analyses were repeated with only the prospective studies (leaving out the retrospective studies). For the dichotomous outcome data, odds ratios (OR) with 95% confidence interval (CI) were calculated, and continuous outcome data were summarized as mean difference and corresponding 95% CI. In the forest plots, the solid squares denote the Peto OR of each individual study, the horizontal lines represent the 95% confidence intervals (CI), and the diamond denotes the cumulative Peto OR.[33] Statistical heterogeneity across studies was assessed using both the chi-squared test with $P < .10$ regarded as significant, and the I^2 statistic assuming heterogeneity if $I^2 > 50\%$.[34]

Results

The electronic search yielded 440 articles from PubMed (n = 146), Embase (n = 155), Web of Science (n = 94), the Cochrane Database of Systematic Reviews (n = 22), and Cochrane Central Register of Controlled Trials (n = 23). And 259 articles remained after removal of obvious duplicates. After screening titles and abstracts, 194 articles were excluded based on inclusion and exclusion criteria. Another 44 articles were excluded after assessment of the full-text article, leaving 21 articles (n = 61,487 patients) for analysis in this review. One meta-analysis including recent literature was found.[35] No additional relevant studies were found in the reference lists of the included studies. The study selection process is presented in Figure 1.

Figure 1. Flow diagram of the study selection process.



Study characteristics

The 21 selected studies included 3 RCTs (n = 321 patients) and 18 nonrandomized comparative cohort studies of which 7 were prospective (n = 1798 patients) and 11 retrospective (n = 59,368 patients). Nineteen studies evaluated 2 of the 3 approaches, 5 comparing the AA with the PA[11, 23, 36-38], 11 the LA with the PA[7, 8, 10, 20, 21, 24, 27, 39-42] and 3 studies compared the AA with the LA[26, 43, 44]. Two studies included all 3 approaches.[45, 46] The mean age of the study populations ranged from 63 to 88 years and 58 to 92% of the patients were female. The follow-up period varied between 1 and 96 months. The study characteristics are listed in Table 1.

Table 1. Characteristics of included studies, by study design.

Author (publication year)	Country	Sample size per approach			Mean age	Sex (%F)	Follow-up (months)
		AA	LA	PA			
Randomized Controlled Trials							
Auffarth (2011)[26]	Austria	24	24	-	83.2	79	6
Parker (2015)[20]	UK	-	108	108	84.0*	92	12
Renken (2012)[44]	Germany	30	27	-	84.0*	88*	1
Prospective Cohort Studies							
Baba (2013)[23]	Japan	40	-	39	75.8*	83	36
Enocson (2008)[27]	Sweden	-	431	308	84.0	80	27.6 (mean)*
Langlois (2015)[36]	France	38	-	44	85.4*	74	21 (SD ±5.0)
Mukka (2016)[21]	Sweden	-	101	83	84.4	70	12
Sayed-Noor (2016)[39]	Sweden	-	24	24	83.0*	81	12
Svenoy (2017)[42]	Norway	-	397	186	82.8	74	12
Tsukada (2010)[37]	Japan	44	-	39	81.1*	82	12
Retrospective Cohort Studies							
Abram (2015)[40]	UK	-	753	54	83.0	71	3-71 (range)
Biber (2012)[24]	Germany	-	217	487	80.4	70	NA
Bush (2007)[38]	USA	186	-	199	79.8	73	6
Carlson (2017)[43]	USA	85	75	-	82.8*	60*	6
Kristensen (2017)[8]	Norway	-	18918	1990	83.0	73	96
Leonardsson (2016)[7]	Nor/Swe	-	1140	978	85.0	74	6-18 (range)
Ozan (2016)[10]	Turkey	-	86	147	78.6*	58	17.1 (mean)*
Pala (2016)[11]	Italy	55	-	54	88.0	80	6
Rogmark (2014)[41]	Sweden	-	20519	11522	84.0	72	32.4*
Sierra (2006)[46]	USA	1432	125	245	63.0	NA	12
Trinh (2015)[45]	USA	31	41	29	80.7	NA	3.7 (mean)*

AA Anterior Approach, LA Lateral Approach, PA Posterior Approach, y years, F female, NA not available, SD Standard Deviation. *Derived and calculated from article data.

Quality assessment

Some risk of bias was present in all studies, as shown in Appendix C. For 2 of the RCTs, a high risk was considered to be present due to 'missing outcome data' (Appendix table C. 1). The non-randomized cohort studies had on average good quality with a moderate risk of confounding in all retrospective studies (Appendix table C. 2). Four of the 7 prospective cohort studies had relatively small sample sizes. Most prospective studies had no blinding of outcome assessments, meaning there was a risk of detection and observer bias in their outcomes. Most of the studies had dislocation rate as the primary outcome, while the secondary outcomes in these studies were often poorly defined.

Eleven studies were retrospective observational studies susceptible to forms of bias inherent to this study design, such as confirmation bias. Although we only included studies with the predominant reason for hemiarthroplasty being traumatic hip fractures in this review, 3 retrospective studies also included a small number of nontraumatic patients.[7, 11, 46]

Surgical outcomes

Operation time and surgical blood loss

Eleven studies reported the operation time of 2 approaches.[8, 11, 20, 21, 23, 26, 36, 37, 42-44] The study by Parker et al. could not be included in the meta-analysis because no standard deviations were reported. The meta-analyses showed no statistically significant difference in the mean operation time when comparing the PA with the AA (mean difference = 3.0 minutes; 95% CI, -8.5 to 14.5; p = 0.61; Fig. 2A) or the LA with the AA (mean difference = -6.5 minutes; 95% CI, -17.8 to 4.7; p = 0.25; Fig. 2C). The difference in operation time for the PA compared to the LA was borderline significant (mean difference = 10.0 minutes; 95% CI, -20.5 to 0.5; p=0.06; Fig. 2B). Parker et al. reported no significant difference in operation time between the LA and the PA.

Ten studies compared surgical blood loss in various ways, including estimated and measured intraoperative blood loss in milliliters, centiliters, and grams, postoperative drop in hemoglobin blood level, transfusion rates, and hematoma formation.[11, 20, 21, 23, 24, 26, 36, 37, 43, 44]

Carlson et al. reported a significant difference in the hemoglobin before and after surgery in favor of the AA vs the LA. This was not evident from the other studies and insufficient data was available for a meta-analysis.[26, 44] Pala et al. reported less surgical blood loss (in centilitres), but a contradicting and significantly larger drop in postoperative haemoglobin levels for the AA than for the PA. Biber et al. reported significantly more postoperative haematoma formation in the LA compared to the PA (p = 0.001) while Mukka et al. and Parker et al. reported no differences in the average surgical blood loss and transfusion rates.[11, 20, 21, 24]

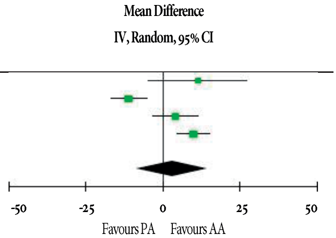
Figure 2. Forest plots comparing the operation time in minutes for (A) the Posterior Approach vs the Anterior Approach, (B) for the Posterior Approach vs the Lateral Approach and (C) for the Lateral Approach vs the Anterior Approach.

(A)

	Posterior approach			Anterior approach				Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Baba 2013	76.7	33.0	39	65.3	39.0	40	18.8%	11.40 [-4.52, 27.32]
Langlois 2015	54.0	15.0	44	65.0	12.0	38	27.3%	-11.00 [-16.85, -5.15]
Tsukada 2010	79.3	15.2	39	75.1	19.2	44	26.2%	4.20 [-3.21, 11.61]
Pala 2016	57.0	12.5	54	47.0	15.0	55	27.7%	10.00 [4.82, 15.18]
Total (95% CI)			**176**			**177**	**100.0%**	**3.01 [-8.50, 14.52]**

Heterogeneity: $Tau^2 = 117.48$; $Chi^2 = 29.82$, df = 3 ($P < 0.00001$); $I^2 = 90\%$

Test for overall effect: Z = 0.51 (P = 0.61)

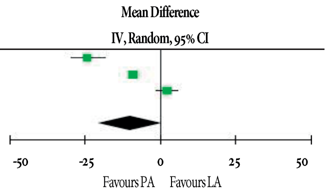


(B)

	Posterior approach			Lateral approach				Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Mukka 2016	66.0	18.0	83	90.0	21.0	101	31.6%	-24.00 [-29.64, -18.36]
Kristensen 2017	67.0	21.0	1990	76.0	25.0	18918	34.8%	-9.00 [-9.99, -8.01]
Svenoy 2017	69.2	20.0	186	66.9	19.0	397	33.6%	2.30 [-1.13, 5.73]
Total (95% CI)			**2259**			**19416**	**100.0%**	**-9.95 [-20.33, 0.44]**

Heterogeneity: $Tau^2 = 80.46$; $Chi^2 = 68.13$, df = 2 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 1.88 (P = 0.06)

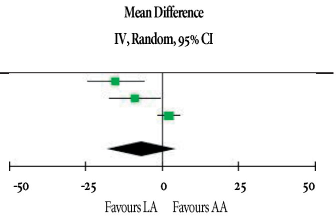


(C)

	Lateral approach			Anterior approach				Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Auffarth 2011	65.3	11.75	24	80.4	19.5	24	30.8%	-15.10 [-24.21, -5.99]
Remken 2012	64.8	17.1	27	73.6	14.4	30	32.0%	-8.80 [-17.06, -0.54]
Carlson 2017	45.3	8.8	75	42.9	13.9	85	37.2%	2.40 [-1.16, 5.96]
Total (95% CI)			**126**			**139**	**100.0%**	**-6.57 [-17.81, 4.66]**

Heterogeneity: $Tau^2 = 84.97$; $Chi^2 = 16.12$, df = 2 ($P = 0.0003$); $I^2 = 88\%$

Test for overall effect: Z = 1.15 (P = 0.25)



SD, standard deviation; CI, confidence interval.

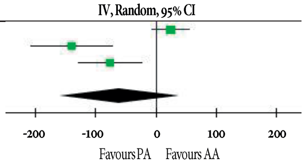
Only 3 studies reported a quantitative measure of mass or volume that could be converted to millilitres of blood loss, to enable a meta-analysis for the PA vs the AA (Fig. 3).[11, 23, 37] No significant difference was observed (mean difference, -60 millilitres; 95% CI, -160 to 39; p = 0.23).

The statistical heterogeneity observed in the outcomes operation time and blood loss between the studies included in these meta-analyses may be attributable to differences in the experience of the surgeons between the studies. In some prospective studies, the patients were only operated by specific surgeons with experience in the used approach.[11, 21] In other studies, surgeons alternated both approaches based on the patient allocation.[23, 36, 37] Both approaches studied by Langlois et al. were performed by unsupervised surgeons in training. Exclusion of this study from the meta-analysis resulted in a comparison with more homogenous study results ($Chi^2 = 1.73$, df = 2, P = .42, $I^2 = 0\%$) and a mean difference in operation time of 8.3 minutes in favour of the AA compared to the PA (95% CI, 4.2 to 12.4; $p < .0001$). Similar methodological reasons for outliers could not be identified for the operation time of the PA compared to the LA and blood loss, although differences in the surgeons' experience between these studies cannot be excluded.

Figure 3. Forest plot comparing surgical blood loss for the Posterior Approach vs the Anterior Approach.

	Posterior approach			Anterior approach				Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Baba 2013	146.0	56.0	39	121.0	82.0	40	35.4%	25.00 [-5.90, 55.90]
Tsukada 2010	230.0	114.9	39	370.1	192.1	44	31.4%	-140.10 [-207.35, -72.85]
Pala 2016	213.0	150.0	54	289.0	130.0	55	33.2%	-76.00 [-128.74, -23.26]
Total (95% CI)			**132**			**139**	**100.0%**	**-60.36 [-159.67, 38.95]**

Heterogeneity: Tau² = 7004.27; Chi² = 24.73, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.19 (P = 0.23)



SD, standard deviation; CI, confidence interval.

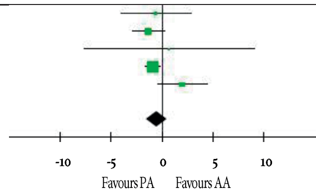
Hospital length of stay

Only Bush and Wilson found a statistically significant difference in the admission time between the PA and AA, the 5 other studies did not.[11, 20, 23, 36, 37] Comparing the pooled results for hospital length of stay time, the PA and AA showed no significant difference (mean difference, -0.54 days; 95% CI, -1.55 to 0.47; p = .29; Fig. 4). Parker et al. compared the hospital length of stay between the PA and LA (mean difference, 1.8 days; p = .40). Carlson et al. reported a significantly shorter hospital length of stay for the AA compared to the LA (mean difference 2.7 days; p < .01).

Figure 4. Forest plot comparing the hospital length of stay for the Posterior Approach vs the Anterior Approach.

	Posterior approach			Anterior approach				Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Baba 2013	29.3	10.25	39	29.9	4.0	40	7.7%	-0.60 [-4.05, 2.85]
Langlois 2015	8.7	4.0	44	10.0	3.3	38	26.0%	-1.30 [-2.88, 0.28]
Tsukada 2010	36.1	21.0	39	35.4	17.4	44	1.4%	0.70 [-7.66, 9.06]
Bush 2007	6.41	3.52	199	7.28	3.98	186	51.0%	-0.87 [-1.62, -0.12]
Pala 2016	14.0	6.75	54	12.0	6.25	55	13.8%	2.00 [-0.44, 4.44]
Total (95% CI)			**375**			**363**	**100.0%**	**-0.54 [-1.55, 0.47]**

Heterogeneity: Tau² = 0.38; Chi² = 5.55, df = 4 (P = 0.24); I² = 28%
Test for overall effect: Z = 1.05 (P = 0.29)



SD, standard deviation; CI, confidence interval.

Complications

Perioperative fractures

One of 13 studies that reported the incidence of perioperative fractures observed that perioperative fractures occurred significantly more often in patients operated using the LA compared to the PA

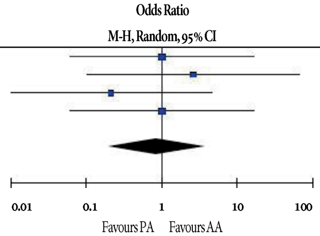
(OR, 1.5; 95% CI, 1.1 to 2.0; p = .03), but this study did not report the patient numbers and could therefore not be included in the meta-analysis.[41] No statistically significant differences were found after pooling data of 4 studies[11, 23, 36, 37] that compared the PA and the AA (OR, 0.87; 95% CI, 0.20 to 3.82; p = .85; Fig. 5A), 5 studies[7, 20, 21, 24, 42] that analyzed the PA and the LA (OR, 1.07; 95% CI, 0.51 to 2.22; p = .87; Fig. 5B) and 3 studies[26, 43, 44] that compared the LA with the AA (OR, 1.13; 95% CI, 0.26 to 4.87; p = .87; Fig. 5C).

Figure 5. Forest plots comparing the incidence of perioperative fractures for (A) the Posterior Approach vs the Anterior Approach, (B) for the Posterior Approach vs the Lateral Approach and (C) for the Lateral Approach vs the Anterior Approach.

(A)

	Posterior approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Baba 2013	1	39	1	40	27.8%	1.03 [0.06, 17.01]
Langlois 2015	1	44	0	38	21.0%	2.66 [0.11, 67.11]
Tsukada 2010	0	39	2	44	23.3%	0.22 [0.01, 4.62]
Pala 2016	1	54	1	55	28.0%	1.02 [0.06, 16.71]
Total (95% CI)		**176**		**177**	**100.0%**	**0.87 [0.20, 3.82]**
Total events	3		4			

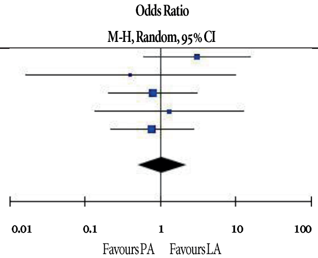
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.29$, df = 3 (P = 0.73); $I^2 = 0\%$
Test for overall effect: Z = 0.19 (P = 0.85)



(B)

	Posterior approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Parker 2015	6	108	2	108	20.5%	3.12 [0.61, 15.80]
Mukka 2016	0	83	1	102	5.2%	0.41 [0.02, 10.08]
Svenoy 2017	3	186	8	397	30.2%	0.80 [0.21, 3.04]
Biber 2012	3	487	1	217	10.5%	1.34 [0.14, 12.94]
Leonardsson 2016	4	978	6	1140	33.6%	0.78 [0.22, 2.76]
Total (95% CI)		**1842**		**1964**	**100.0%**	**1.07 [0.51, 2.22]**
Total events	16		18			

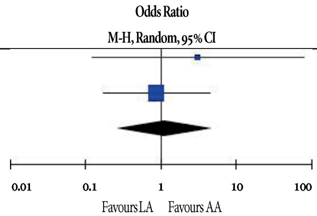
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.49$, df = 4 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 0.17 (P = 0.87)



(C)

	Lateral approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Auffarth 2011	1	24	0	24	20.1%	3.13 [0.12, 80.68]
Renken 2012	0	27	0	30		Not estimable
Carlson 2017	3	85	3	75	79.9%	0.88 [0.17, 4.49]
Total (95% CI)		**136**		**129**	**100.0%**	**1.13 [0.26, 4.87]**
Total events	4		3			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, df = 1 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.17 (P = 0.87)



SD, standard deviation; CI, confidence interval.

Wound infections

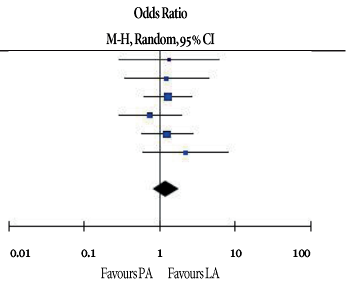
Two of 3 studies comparing the PA with the AA reported no cases of wound infections in either group, so no meta-analysis could be performed. The third study reported no significant difference.[23, 36, 37] None of the 7 studies that compared wound infections between the PA and the LA reported a significant difference in wound infections.[7, 10, 20, 21, 24, 41, 42] Rogmark et al. reported an OR of 0.8 (95% CI, 0.7 to 1.0; p = .05) but no patient numbers, and could therefore not be included in the meta-analysis. The pooled incidence indicated no difference in the risk of infections between the PA vs the LA (OR, 1.23; 95% CI, 0.82 to 1.84; p = .31; Fig. 6A). No significant difference in infection rate was found in the individual studies and in the meta-analysis comparing the LA and the AA (OR, 1.26; 95% CI, 0.24 to 6.67; p = .78; Fig. 6B).[26, 43, 44]

Figure 6. Forest plot comparing the incidence of wound infections for (A) the Posterior Approach vs the Lateral Approach and (B) for the Lateral Approach vs the Anterior Approach.

(A)

	Posterior approach		Lateral approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Parker 2015	4	108	3	108	7.0%	1.35 [0.29, 6.16]
Mukka 2016	5	83	5	102	9.9%	1.24 [0.35, 4.45]
Svenoy 2017	12	186	20	397	29.7%	1.30 [0.62, 2.72]
Biber 2012	12	487	7	217	18.0%	0.76 [0.29, 1.95]
Leonardsson 2016	13	978	12	1140	25.9%	1.27 [0.58, 2.79]
Ozan 2016	11	147	3	86	9.5%	2.24 [0.61, 8.26]
Total (95% CI)		**1989**		**2050**	**100.0%**	**1.23 [0.82, 1.84]**
Total events	57		50			

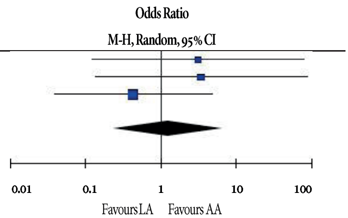
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.86$, df = 5 (P = 0.87); $I^2 = 0\%$
Test for overall effect: Z = 1.01 (P = 0.31)



(B)

	Lateral approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Auffarth 2011	1	24	0	24	26.3%	3.13 [0.12, 80.68]
Renken 2012	1	27	0	30	26.4%	3.45 [0.13, 88.40]
Carlson 2017	1	85	2	75	47.3%	0.43 [0.04, 4.89]
Total (95% CI)		**136**		**129**	**100.0%**	**1.26 [0.24, 6.67]**
Total events	3		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.42$, df = 2 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.27 (P = 0.78)



SD, standard deviation; CI, confidence interval.v

Dislocations

Nineteen out of the 21 included studies reported the dislocation incidence after surgery. Fifteen of these compared the PA with one of the other approaches (5 with the AA[11, 23, 36-38], 10 with the LA, of which 9 available for the meta-analysis[7, 10, 20, 21, 24, 27, 39-42] and 2 compared all 3 approaches[45, 46]). Two studies compared the LA with the AA of which one reported no cases of dislocations in either group.[43, 44]

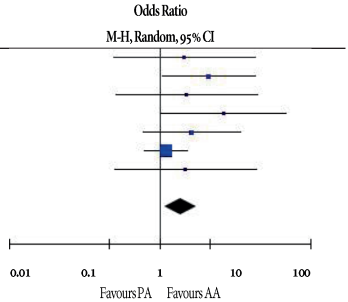
In the meta-analyses, the incidence of dislocations after the PA was higher than after the AA (OR, 2.61; 95% CI, 1.26 to 5.43; p = .01; Fig. 7A) and after the LA (OR, 2.90; 95% CI, 1.63 to 5.14; p = .0003; Fig. 7B). Four studies compared the dislocation rate between the LA and AA.[43-46] In the meta-analysis an OR of 1.87 (95% CI, 0.77 to 4.55; p = .17; Fig. 7C) was found for dislocation after the LA compared to the AA.

Figure 7. Forest plots comparing the dislocation rate for (A) the Posterior Approach vs the Anterior Approach, (B) for the Posterior Approach vs the Lateral Approach and (C) for the Lateral Approach vs the Anterior Approach.

(A)

	Posterior approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Baba 2013	1	39	0	40	5.1%	3.16 [0.12, 79.85]
Langlois 2015	9	44	1	38	11.9%	9.51 [1.15, 79.03]
Tsukada 2010	1	39	0	44	5.1%	3.47 [0.14, 87.62]
Bush 2007	9	199	0	186	6.6%	18.60 [1.07, 321.88]
Pala 2016	4	54	1	55	10.8%	4.32 [0.47, 39.97]
Sierra 2006	5	245	22	1432	55.5%	1.34 [0.50, 3.56]
Trinh 2015	1	29	0	31	5.1%	3.32 [0.13, 84.70]
Total (95% CI)		**649**		**1826**	**100.0%**	**2.61 [1.26, 5.43]**
Total events	30		24			

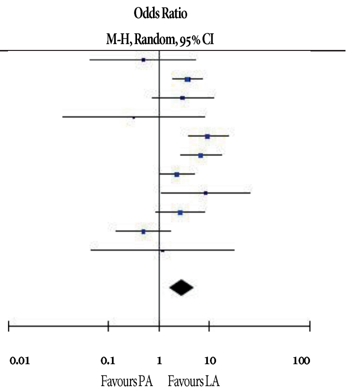
Heterogeneity: Tau² = 0.00; Chi² = 5.86, df = 6 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)



(B)

	Posterior approach		Lateral approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Parker 2015	1	108	2	108	4.3%	0.50 [0.04, 5.55]
Enocson 2008	32	305	13	431	15.2%	3.77 [1.94, 7.31]
Mukka 2016	7	83	3	102	9.0%	3.04 [0.76, 12.14]
Sayed-Noor 2016	0	24	1	24	2.7%	0.32 [0.01, 8.25]
Svenoy 2017	24	186	6	397	12.8%	9.65 [3.87, 24.06]
Abram 2015	7	54	16	753	12.6%	6.86 [2.69, 17.49]
Leonardsson 2016	20	978	10	1140	14.2%	2.36 [1.10, 5.06]
Biber 2012	19	487	1	217	5.7%	8.77 [1.17, 65.93]
Ozan 2016	17	147	4	86	11.0%	2.68 [0.87, 8.25]
Sierra 2006	5	245	5	125	9.9%	0.50 [0.14, 1.76]
Trinh 2015	1	29	0	11	2.6%	1.21 [0.05, 31.95]
Total (95% CI)		**2646**		**3394**	**100.0%**	**2.90 [1.63, 5.14]**
Total events	133		61			

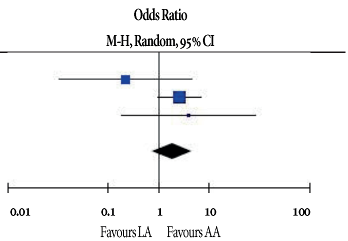
Heterogeneity: Tau² = 0.45; Chi² = 22.95, df = 10 (P = 0.01); I² = 56%
Test for overall effect: Z = 3.64 (P = 0.0003)



(C)

	Lateral approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Renken 2012	0	27	0	30		Not estimable
Carlson 2017	0	75	2	85	37.3%	0.22 [0.01, 4.68]
Sierra 2006	5	125	22	1432	54.2%	2.67 [0.99, 7.18]
Trinh 2015	2	41	0	31	8.5%	3.99 [0.18, 86.09]
Total (95% CI)		**268**		**1578**	**100.0%**	**1.87 [0.77, 4.55]**
Total events	7		24			

Heterogeneity: Chi² = 2.61, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.38 (P = 0.17)



SD, standard deviation; CI, confidence interval.

Reoperation rate

In the selected studies, reoperations included among others closed and open reduction of dislocations, revision arthroplasties, fixation of perioperative fractures, and capsular repair after repetitive dislocations. Only Langlois et al. compared the reoperation rates of the PA with the AA.[36] No significant differences have been reported in recent literature on the long-term prosthesis survival between the AA and PA.[11, 36]

Rogmark et al. reported a statistically significant difference in the reoperation rate of the PA compared the LA in favour of the LA.[41] The meta-analysis including 4 studies showed a significant result in favour of the LA (OR, 1.25; 95% CI, 1.12 to 1.41; $p < .0001$; Fig. 8A).[7, 20, 21, 41] This result was mostly due to the large number of patients in the study by Rogmark et al., with a weight of more than 90% in the meta-analysis. The meta-analysis comparing the LA with the AA included 3 studies and indicated no significant difference (OR, 1.54; 95% CI, 0.50 to 4.77; $p = .45$; Fig. 8B).[26, 43, 44]

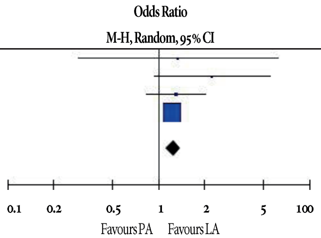
When repeating the meta-analyses including only the studies with a prospective design, the outcomes were similar to those of the meta-analyses that also included the retrospective studies. These outcomes are not included in this publication, but are available upon request.

Figure 8. Forest plot comparing the reoperation rate for (A) the Posterior Approach vs the Lateral Approach and (B) for the Lateral Approach vs the Anterior Approach.

(A)

	Posterior approach		Lateral approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Parker 2015	4	108	3	108	0.6%	1.35 [0.29, 6.16]
Mukka 2016	15	83	9	102	1.7%	2.28 [0.94, 5.52]
Leonardsson 2016	40	978	36	1140	6.2%	1.31 [0.83, 2.07]
Rogmark 2014	477	11999	687	21206	91.6%	1.24 [1.10, 1.39]
Total (95% CI)		**13168**		**22556**	**100.0%**	**1.25 [1.12, 1.41]**
Total events	536		735			

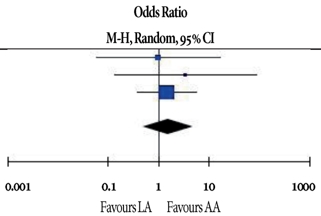
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.85$, $df = 3$ ($P = 0.60$); $I^2 = 0\%$
Test for overall effect: $Z = 3.89$ ($P < 0.0001$)



(B)

	Lateral approach		Anterior approach			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Auffarth 2011	1	24	1	24	19.5%	1.00 [0.06, 16.97]
Renken 2012	1	27	0	30	9.2%	3.45 [0.13, 88.40]
Carlson 2017	5	75	4	85	71.3%	1.45 [0.37, 5.60]
Total (95% CI)		**126**		**139**	**100.0%**	**1.54 [0.50, 4.77]**
Total events	7		5			

Heterogeneity: $Chi^2 = 0.34$, $df = 2$ ($P = 0.85$); $I^2 = 0\%$
Test for overall effect: $Z = 0.75$ ($P = 0.45$)



SD, standard deviation; CI, confidence interval.

Patient reported outcomes

Pain

Postoperative pain was rated in 7 studies.[7, 8, 11, 21, 26, 36, 39] Because the studies used different methods including the Visual Analogue Scale, Numeric Rating Scale (NRS) scores, and the use of analgesic medication at various intervals after surgery, the results could not be pooled. Auffarth et al. and Renken et al. both reported significant, contradicting results comparing the AA and LA. Pala et al. reported significantly more pain on the first postoperative days after the AA than after the PA. From day 4 onwards results were similar for the AA and PA.[36] Two other studies compared the long-term pain perception of patients for the LA and the PA, which was significantly better for the PA.[7, 8]

Functionality

Nine studies assessed the patients' functionality using several different Patient Reported Outcome Measures (PROMS), such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Barthel Index or the Harris Hip Score (HHS).[8, 21, 23, 26, 36, 37, 39, 43, 44] Four of these studies reported the HHS, but after varying intervals up to one-year after surgery.[21, 26, 37, 39] Therefore, a meta-analysis of these results was not feasible.

Only Tsukada and Wakui reported statistically significant differences in the HHS in favour of the AA compared to the PA after 2 months.[37] However, this difference was no longer significant after 4 months. The benefit in short-term functionality of the AA vs PA was also found in the study of Baba et al., who reported the unaided walking ability measured with a 4-category mobility score after 2 weeks.[23] Similar to the study by Tsukada and Wakui, the reported difference in functionality was no longer significant after 6 months.

Regarding a comparison between the PA and LA, significantly more patients walked with a limp and suffered from a positive Trendelenburg sign after the LA in the study by Sayed-Noor et al. but this study showed no significant difference in the HHS after 12 months.[39] Only Kristensen et al. reported a long-term difference in functionality with a significant difference up to 3 years in favour of the PA over the LA.[8] Only 1 of 3 studies that compared functional outcome between the AA and LA reported a significant difference in the short-term postoperative mobility, in favour of the AA.[26, 43, 44]

Quality of life

Only 3 studies reported on aspects of the patient-reported quality of life such as patient satisfaction or general health-related quality of life measured with the EuroQol-5D.[7, 8, 39] All 3 studies compared the LA with the PA, but only the largest study showed significant differences in the EuroQol-5D in favour of the PA, also after adjusting for confounding variables.[8]

Discussion

This meta-analysis aimed at analyzing the available evidence on compared outcomes after 3 conventional surgical access routes for hemiarthroplasty in proximal femoral fractures, in order to identify the superior surgical approach. It is the first meta-analysis to compare all 3 major groups of approaches with each of the other.

Most notably, many studies had dislocation as primary outcome and compared the PA to either the AA or LA. Statistically significant differences were observed in each comparison with the lowest risk of dislocation after surgery using the AA and highest after use of the PA. The outcome of the meta-analyses is significant for each of the comparisons with the PA, with little heterogeneity in the data. Higher dislocation rates are described in literature regardless of posterior capsule repair and dislocations are the most frequent cause for reoperations and revisions of a hemiarthroplasty.[21, 27] Our meta-analysis for reoperations supports the latter, indicating a higher reoperation risk for the PA compared to the LA.[7] The elevated risk of dislocation after the PA and the associated increased risk of reoperation seem the most apparent of all outcomes studied in this meta-analysis. In this respect, the PA may be regarded as an inferior approach compared to the AA and LA, which pleads against the routine use of this approach for hemiarthroplasty. Especially in older patients, these complications cause significant morbidity. Surgeons in training may want to focus on the AA or LA for regular use in hemiarthroplasty.

The pooled data indicate a shorter operation time with the PA compared to the LA and hint at a shorter operation time for the AA compared to the PA for experienced surgeons. However, large heterogeneity was observed and the clinical relevance in the treatment of femoral neck fractures is questionable. Large statistical heterogeneity was also observed for the surgical blood loss between the studies. These surgical outcomes in general have a strong correlation with the experience of the surgical team[36, 47-49] and with the technical difficulty of the procedure.[11, 37] This stresses that the outcomes of these operations are optimized in the hands of experienced and dedicated surgeons.

Studies report a longer learning curve for the AA, claiming that this procedure is technically more difficult to perform.[11] Consequently, the AA is also associated in some studies with higher risks for complications such as greater trochanteric fractures and nerve damage, more blood loss and a longer operation time in some studies, though this is not evident from our meta-analyses.[11, 36, 37] A shorter hospital length of stay was found for the AA vs the LA.[43] No other significant differences were found based on the available data and pooled analyses for the hospital length of stay, the incidence of wound infections and perioperative fractures.

Data on patient-reported function in several studies could not be pooled because different assessments were used on different time points. However, a review of the data suggests better short-term functional outcomes using the AA compared to the PA.[23, 36, 37] Many studies agree that the apparent functional benefit of the AA compared the other approaches is of major clinical importance.[26, 44, 45] Although no significant long-term differences were reported, a better short-term mobility could be deterministic for the rehabilitation strategy. Patients with a faster recovery can be discharged earlier, which Carlson et al. may indicate with a shorter hospital length of stay after the AA compared to the LA.[45] This could mean an increase in postoperative self-dependence, fewer admissions to rehabilitation homes and a decrease of health-care costs. However, the current findings are inconclusive and more well-designed studies are needed to confirm these assumptions.

Overall complication rates[11, 20, 21, 24, 36] and mortality rates[10, 20, 24, 36, 45] found in recent literature did not report any significant differences correlated to the surgical approach.

Our conclusions in respect to the dislocation rates and functionality are similar to a previous meta-analysis on the anterior approach.[35]

The large Scandinavian surveys suggest a lower postoperative quality of life after the LA compared to the PA, attributed to gluteus medius muscle insufficiency associated with the LA.[7, 8] However, the study by Sayed-Noor et al. indicates that the high prevalence of a Trendelenburg sign and limp does not affect the clinical outcome. The studies by Leonardsson et al. and Kristensen et al. on the postoperative quality of life may have been susceptible to sampling bias, because their methodology excluded a disproportionate number of cognitively impaired patients.[7, 8] Dementia is prevalent in up to 85% percent of the older hip fracture population[50], and is considered a major risk factor for hemiarthroplasty dislocation.[23, 51] In the predominantly older hip fracture patient population, patient-reported outcome measures may be biased towards fitter patients. Kristensen et al. concludes that despite the increased risk for dislocations, the PA results in a favourable quality of life, but this should be specified for mentally competent patients who comprehend their movement restrictions.

Limitations

Only 3 RCTs were eligible for inclusion in this meta-analysis. All other included studies were comparative cohort studies with a moderate risk of bias. Additionally, the retrospective studies included far more patients compared to the prospective studies, weighing heavier in the results of all meta-analyses. However, similarity in the outcomes of the meta-analysis with and without the retrospective studies indicates a degree of reliability for the retrospective methodology to study surgical outcomes.

Besides previously stated causes of the statistical heterogeneity found in the pooled data, differences between the studies were observed regarding the implant type, the ratio of cemented and uncemented arthroplasties, rehabilitation strategies and the length of follow-up period. For our study, we pooled conventional approaches with similar technical and anatomical variations in 3 main approach groups (AA, LA and PA), assuming that the surgical techniques within each of the 3 main groups render similar outcomes. This assumption was not studied and differences in outcomes cannot be ruled out.

Also, differences in the methods of treatment and outcome assessment were observed between the included studies, so that meta-analysis of clinically relevant treatment outcomes such as functionality and postoperative pain could not be performed. Our study pooled the technical and anatomical similar varieties on conventional approaches to form 3 main approach groups (AA, LA and PA). Clinically relevant differences in the treatment outcomes between the surgical techniques within each of the 3 main groups are poorly studied, but can't be ruled out. Such differences for example, have been found in pain and mobility for the anterolateral and direct lateral approach[52], but not for the posterior minimal invasive surgery vs the conventional posterior approach[53].

Finally, only a few studies were available for comparisons with the LA. Given these limitations, more well-designed studies are needed to confirm the findings presented in this meta-analysis. Detailed analyses of national datasets such as the Swedish Hip Arthroplasty Register, the National Joint Registry for England and Wales and the Dutch Hip Fracture Audit could provide additional insight in the treatment outcomes of various approaches.

Conclusions

The PA demonstrates an increased risk of dislocation and re-operation compared to the LA and AA. No advantages of the posterior approach were found that might counterbalance the disadvantage of the increased dislocation risk. Its use for fracture related hemiarthroplasty is therefore questionable. Based on the current literature, the LA and AA have comparable outcomes in terms of surgical outcomes and complications, so that one cannot be preferred over the other. The AA may be related to faster recovery in terms of better short-term functional outcomes compared to the PA and earlier discharged compared to the LA. High quality comparative studies are needed to further substantiate the preferred anatomical route for hemiarthroplasty in older femoral neck fracture patients.

Appendices

Appendix A

Search strategy (PubMed)

((“Hip Fractures”[Mesh] OR “hip fracture”[tw] OR “hip fractures”[tw] OR “femoral neck fracture”[tw] OR “femoral neck fractures”[tw] OR “collum fracture”[tw] OR “collum fractures”[tw] OR “collum femoris fracture”[tw] OR “collum femoris fractures”[tw] OR “proximal femur fracture”[tw] OR “proximal femur fractures”[tw] OR “intertrochanteric fracture”[tw] OR “intertrochanteric fractures”[tw] OR “inter trochanteric fracture”[tw] OR “inter trochanteric fractures”[tw] OR “subtrochanteric fracture”[tw] OR “subtrochanteric fractures”[tw] OR “sub trochanteric fracture”[tw] OR “sub trochanteric fractures”[tw]) AND (“Hip Prosthesis”[Mesh] OR “Arthroplasty, Replacement, Hip”[Mesh] OR “prosthesis”[tw] OR prosthe*[tw] OR “arthroplasty”[tw] OR “hemiarthroplasty”[tw] OR arthroplast*[tw] OR hemiarthroplast*[tw] OR “BHH”[tw])) AND (((“anterior”[tw] OR anterior*[tw] OR “anterior approach”[tw] OR “true anterior”[tw] OR “direct anterior approach”[tw] OR “DAA”[tw] OR “smith-petersen”[tw] OR “smith petersen”[tw] OR “smithpetersen”[tw] OR “ASI”[tw] OR “AMIS”[tw]) AND (“anterolateral”[tw] OR “antero lateral”[tw] OR anterolateral*[tw] OR antero lateral*[tw] OR “Watson-Jones”[tw] OR “Watson Jones”[tw] OR “watsonjones”[tw])) OR ((“anterior”[tw] OR anterior*[tw] OR “anterior approach”[tw] OR “true anterior”[tw] OR “direct anterior approach”[tw] OR “DAA”[tw] OR “smith-petersen”[tw] OR “smith petersen”[tw] OR “smithpetersen”[tw] OR “ASI”[tw] OR “AMIS”[tw]) AND (“lateral”[tw] OR lateral*[tw] OR “lateral approach”[tw] OR “direct lateral approach”[tw] OR “Hardinge”[tw] OR “transgluteal”[tw] OR transglutea*[tw] OR “trans gluteal”[tw] OR trans glutea*[tw] OR “transtrochanteric”[tw] OR transtrochanter*[tw] OR “trans trochanteric”[tw] OR trans trochanter*[tw] OR “McFarland and Osborne”[tw])) OR ((“anterior”[tw] OR anterior*[tw] OR “anterior approach”[tw] OR “true anterior”[tw] OR “direct anterior approach”[tw] OR “DAA”[tw] OR “smith-petersen”[tw] OR “smith petersen”[tw] OR “smithpetersen”[tw] OR “ASI”[tw] OR “AMIS”[tw]) AND (“posterior”[tw] OR posterior*[tw] OR “posterolateral”[tw] OR posterolater*[tw] OR “postero lateral”[tw] OR postero lateral*[tw] OR “back”[tw] OR “Moore”[tw] OR “Southern”[tw])) OR ((“anterior”[tw] OR anterior*[tw] OR “anterior approach”[tw] OR “true anterior”[tw] OR “direct anterior approach”[tw] OR “DAA”[tw] OR “smith-petersen”[tw] OR “smith petersen”[tw] OR “smithpetersen”[tw] OR “ASI”[tw] OR “AMIS”[tw]) AND (“minimal invasive”[tw] OR minimal invasiv*[tw] OR “minimally invasive”[tw] OR minimally invasiv*[tw] OR “two-incision”[tw] OR “two incision”[tw] OR two-incision*[tw] OR two incision*[tw] OR “2-incision”[tw] OR “2 incision”[tw] OR 2-incision*[tw] OR 2 incision*[tw] OR “Minimally Invasive Surgical Procedures”[Mesh])) OR ((“anterolateral”[tw] OR “antero lateral”[tw] OR anterolateral*[tw] OR antero lateral*[tw] OR “Watson-Jones”[tw] OR “Watson

Jones"[tw] OR "watsonjones"[tw]) AND ("lateral"[tw] OR lateral*[tw] OR "lateral approach"[tw] OR "direct lateral approach"[tw] OR "Hardinge"[tw] OR "transgluteal"[tw] OR transglutea*[tw] OR "trans gluteal"[tw] OR trans glutea*[tw] OR "transtrochanteric"[tw] OR transtrochanter*[tw] OR "trans trochanteric"[tw] OR trans trochanter*[tw] OR "McFarland and Osborne"[tw])) OR (("anterolateral"[tw] OR "antero lateral"[tw] OR anterolateral*[tw] OR antero lateral*[tw] OR "Watson-Jones"[tw] OR "Watson Jones"[tw] OR "watsonjones"[tw]) AND ("posterior"[tw] OR posterior*[tw] OR "posterolateral"[tw] OR posterolater*[tw] OR "postero lateral"[tw] OR postero lateral*[tw] OR "back"[tw] OR "Moore"[tw] OR "Southern"[tw])) OR (("anterolateral"[tw] OR "antero lateral"[tw] OR anterolateral*[tw] OR antero lateral*[tw] OR "Watson-Jones"[tw] OR "Watson Jones"[tw] OR "watsonjones"[tw]) AND ("minimal invasive"[tw] OR minimal invasiv*[tw] OR "minimally invasive"[tw] OR minimally invasiv*[tw] OR "two-incision"[tw] OR "two incision"[tw] OR two-incision*[tw] OR two incision*[tw] OR "2-incision"[tw] OR "2 incision"[tw] OR 2-incision*[tw] OR 2 incision*[tw] OR "Minimally Invasive Surgical Procedures"[Mesh])) OR (("lateral"[tw] OR lateral*[tw] OR "lateral approach"[tw] OR "direct lateral approach"[tw] OR "Hardinge"[tw] OR "transgluteal"[tw] OR transglutea*[tw] OR "trans gluteal"[tw] OR trans glutea*[tw] OR "transtrochanteric"[tw] OR transtrochanter*[tw] OR "trans trochanteric"[tw] OR trans trochanter*[tw] OR "McFarland and Osborne"[tw]) AND ("posterior"[tw] OR posterior*[tw] OR "posterolateral"[tw] OR posterolater*[tw] OR "postero lateral"[tw] OR postero lateral*[tw] OR "back"[tw] OR "Moore"[tw] OR "Southern"[tw])) OR (("lateral"[tw] OR lateral*[tw] OR "lateral approach"[tw] OR "direct lateral approach"[tw] OR "Hardinge"[tw] OR "transgluteal"[tw] OR transglutea*[tw] OR "trans gluteal"[tw] OR trans glutea*[tw] OR "transtrochanteric"[tw] OR transtrochanter*[tw] OR "trans trochanteric"[tw] OR trans trochanter*[tw] OR "McFarland and Osborne"[tw]) AND ("minimal invasive"[tw] OR minimal invasiv*[tw] OR "minimally invasive"[tw] OR minimally invasiv*[tw] OR "two-incision"[tw] OR "two incision"[tw] OR two-incision*[tw] OR two incision*[tw] OR "2-incision"[tw] OR "2 incision"[tw] OR 2-incision*[tw] OR 2 incision*[tw] OR "Minimally Invasive Surgical Procedures"[Mesh])) OR (("posterior"[tw] OR posterior*[tw] OR "posterolateral"[tw] OR posterolater*[tw] OR "postero lateral"[tw] OR postero lateral*[tw] OR "back"[tw] OR "Moore"[tw] OR "Southern"[tw]) AND ("minimal invasive"[tw] OR minimal invasiv*[tw] OR "minimally invasive"[tw] OR minimally invasiv*[tw] OR "two-incision"[tw] OR "two incision"[tw] OR two-incision*[tw] OR two incision*[tw] OR "2-incision"[tw] OR "2 incision"[tw] OR 2-incision*[tw] OR 2 incision*[tw] OR "Minimally Invasive Surgical Procedures"[Mesh]))) NOT ("Animals"[mesh] NOT "Humans"[mesh]) AND (english[la] OR dutch[la]) NOT ("THA"[ti] OR "total hip"[ti] OR "total hips"[ti])

Appendix B

Raw extracted data of treatment outcomes.

Appendix table B.1 Mean operation time.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Average operative time (min)	80.4 (45-123; SD ±**19.5**)	65.3 (45-92; SD ±**11.75**)	-	0.022
Renken (2012)	Skin to skin time (min)	73.6 (SD ±14.4)	64.8(SD ±17.1)	-	ns
Carlson (2017)	Length of surgery (min)	42.9 (SD ±13.9)	45.3 (SD ±8.8)	-	*<0.1*
Baba (2013)	Duration of surgery (min)	65.3 (SD ±39)	-	76.7 (SD ±33)	NA
Langlois (2015)	Operative time (min)	65 (SD ±12)	-	54 (SD ±15)	*0.005*
Pala (2016)	Mean surgery time (min)	47 (20-80; SD ±**15**)	-	57 (30-80; SD ±**12.5**)	*0.001*
Tsukada (2010)	Duration of surgery (min)	75.1 (SD ±19.2)	-	79.3 (SD ±15.2)	0.27
Kristensen (2017)	Operation time (min)	-	76 (SD ±25)	67 (SD ±21)	*<0.001*
Mukka (2016)	Surgical time (min)	-	90 (SD ±21)	66 (SD ±18)	NA
Parker (2015)	Operative time (min)	-	53.6	54.0	0.8
Svenoy (2017)	Mean duration of surgery (min)	-	**66.9 (SD ±19)**	69.2 (SD ±20)	NA

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.2 Mean surgical blood loss.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Perioperative blood loss (haemoglobin trend)	NA	NA	-	0.30
	Postoperative hematoma (n)	4/24	2/24	-	NA
	Intra- and postoperative transfusions	NA	NA	-	0.21
Renken (2012)	Transfusions during study period (mean)	1.1 (SD ±1.4)	1.7 (SD ±3.5)	-	0.44
	Haemoglobin postop (g/l)	110.5 (SD ±16.3)	105.0 (SD ±15.0)	-	ns
Carlson (2017)	Difference in haemoglobin (g/dL)	2.3 (SD ±1.1)	3.0 (SD ±1.3)	-	*<0.01*
	Transfusions (n)	15/85	18/75	-	0.30
Baba (2013)	Intraoperative blood loss (gr)	121 (SD ±82)	-	146 (SD ±56)	NA

Appendix table B.2 Mean surgical blood loss. (continued)

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Langlois (2015)	Drop in haemoglobin (g/dL)	3.0 (SD ±3.4)	-	3.1 (SD ±3.9)	0.9
	Transfusion required (%)	36	-	42	0.8
Pala (2016)	Mean blood loss in drainage (cc)	289 (80-600; SD **±130**)	- -	213 (0-600; SD **±150**)	*0.06* *0.02*
	Haemoglobin difference preoperative and on the first postoperative day (g/dL)	1.5 (0-5.4)	-	1.9 (0-4)	NA
Tsukada (2010)	Blood loss during surgery (ml)	370.1 (SD ±192.1)	-	230 (SD ±114.9)	*0.0002*
Biber (2012)	Postoperative haematoma (%)	-	5.5 (SD ±3.1)	1.2 (SD ±1.0)	*0.001*
Mukka (2016)	Blood loss (unit NA)	-	254 (SD ±141)	239 (SD ±186)	NA
Parker (2015)	Transfusions n (%)	-	14 (13.2%)	21 (19.8%)	0.3
	Mean units blood transfused		0.19	0.31	0.2

Italic font indicates statistical significance ($p < .05$). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.3 Fractures.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Intraoperative femoral shaft fracture	0/24	1/24	-	NA
Carlson (2017)	Periprosthetic fractures	3/85	3/75	-	NA
Baba (2013)	Fractures (femoral greater trochanter and calcar)	1/40	-	1/39	NA
Langlois (2015)	Intraoperative fractures	0/38	-	1/44	NA
Pala (2016)	Periprosthetic fractures	0/55	-	1/54 (1.8%)	NA
	Great trochanter fractures	1/55 (1.8%)	-	0/54	NA
Tsukada (2010)	Greater trochanteric fractures	2/44	-	0/39	NA
Biber (2012)	Perioperative fracture; fractures occurring intraoperatively or early postoperatively	-	0.5% (SD ±0.9)	0.6% (SD ±0.7)	0.80
		-	**1/217**	**3/487**	
Mukka (2016)	Peri-prosthetic fracture	-	1/102	0/83	NA
Leonardsson (2016)	Fracture as a reason for re-operation	-	6/1140 (0.5%)	4/978 (0.4%)	0.7
Parker (2015)	Small operative fracture femur (fracture of the greater trochanter that required no specific treatment)	-	6/108 (5.7%)	1/108 (0.9%)	0.1

Appendix table B.3 Fractures. (continued)

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
	Large operative fracture femur (fracture at the level of the lesser trochanter requiring cerclage wiring)	-	0/108 (0.0%)	1/108 (0.9%)	1.0
	Cumulative small and large fractures	-	**6/108**	**2/108**	
Rogmark (2014)	Periprosthetic fractures as a risk factor for reoperation (HR)	-	1.0	1.5 (1.1-2.0)	*0.03*
Svenoy (2017)	Perioperative fractures	-	3/186 (2%)	8/397 (2%)	0.74

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available..

Appendix table B.4 Wound infections.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Deep wound infection	0/24	1/24	-	NA
Carlson (2017)	Periprosthetic infection	1/85	2/75	-	NA
Baba (2013)	Infection of the superficial layer or deep area	0/40	-	0/39	NA
Langlois (2015)	Deep surgical-site infection	0/38	-	1/44	NA
Tsukada (2010)	Deep infection	0/44	-	0/39	NA
Biber (2012)	Infection (%)	-	3.2 (SD ±2.4)	2.5 (SD ±1.4)	0.57
	-	-	**7/217**	**12/487**	
Leonardsson (2016)	Infection as a reason for re-operation	-	12/1140 (1.1%)	13/978 (1.3%)	0.56
Mukka (2016)	Postoperative deep infection rate	-	5/102	5/83	NA
Ozan (2016)	Postoperative infections	-	3/86 (3.4%)	11/147 (7.4%)	0.737
Parker (2015)	Superficial wound infection	-	3/108	2/108	1.0
	Deep wound infection	-	0/108	2/108	0.5
	Cumulative superficial and deep wound infections	-	**3/108**	**4/108**	
Rogmark (2014)	Infections as a risk factor for reoperation (HR)	-	1.0	0.8 (0.7-1.0)	*0.05*
Svenoy (2017)	Surgical site infection	-	20/397 (5%)	12/186 (6%)	0.49

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.5 Dislocations.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Renken (2012)	Dislocation	0/30	0/27	-	NA
Carlson (2017)	Dislocation	2/82	0/85	-	NA
Baba (2013)	Dislocation rate	0/40	-	1/39	NA
Bush (2007)	Dislocation instability events	0/198	-	9/199 (4.5%)	*0.0033*
Langlois (2015)	Dislocation rate	1/38	-	9/44	*0.02*
Pala (2016)	Dislocation rate	1/55 (1.8%)	-	4/54 (7.4%)	NA
Tsukada (2010)	Dislocations	0/44	-	1/39	0.28
Abram (2015)	Dislocations	-	16/753	7/54	*<0.001*
Biber (2012)	Arthroplasty dislocation, either occurring during inpatient treatment or causing readmission	-	0.5% (SD ±0.9) **1/217**	3.9% (SD ±1.7) **19/487**	*0.01*
Enocnson (2008)	Dislocation rate	-	13/152 (3%)	**32/305 (10.5%)**	*<0.001*
Leonardsson (2016)	Open reduction of a dislocated	-	10/1140 (0.9%)	20/978 (2%)	*0.02*
Mukka (2016)	Single prosthetic dislocation	-	2/102	1/83	NA
	Recurrent prosthetic dislocation	-	1/102	6/83	NA
	Cumulative single and recurrent prosthetic dislocations	-	**3/102**	**7/83**	
Parker (2015)	Dislocation rate	-	2/108 (1.9%)	1/108 (0.9%)	1.0
Rogmark (2014)	Dislocations as a risk factor for reoperation (HR)	-	1.0	2.2 (1.8-2.6)	*0.001*
Ozan (2016)	Postoperative dislocations	-	4/86 (4.6%)	17/147 (11.5%)	0.409
Sayed-Noor (2016)	Dislocations	-	1/24	0/24	NA
Svenoy (2017)	Prosthetic dislocations	-	4/397 (1%)	15/186 (8%)	*<0.001*
	Recurrent dislocations	-	2/397 (0.5%)	9/186 (5%)	*0.001*
Sierra (2006)	Dislocations	22/1432	5/125	5/245	NA
Trinh (2015)	Dislocations	0/31	**2/41**	1/29	NA

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.6 Reoperation rate.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Revision surgery	1/24	1/24	-	

Appendix table B.6 Reoperation rate. (continued)

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Carlson (2017)	Reoperations	4/85 (4.7%)	5/75 (6.7%)	-	0.57
Langlois (2015)	Revision surgery after dislocations	1/38	-	1/44	NA
Leonardsson (2016)	All open reoperations during study period	-	36/1140 (3%)	40/978 (4%)	0.25
Mukka (2016)	Number of hips with any reoperation	-	9/102 (8.8%)	15/83 (18.1%)	NA
	Adjusted OR for reoperations	-	0.42 (CI 0.16-1.11)	1.0	0.08
Parker (2015)	Reoperations (revision arthroplasty, girdlestone and fixation fracture)	-	**3/108**	**4/108**	NA
Rogmark (2014)	Reoperation rates	-	687/21206 (3.2%)	477/11999 (4.0%)	NA
	Surgical approach as a risk factor for reoperation (HR)	-	1.0	1.4 (CI 1.2-1.8)	*0.001*
Kristensen (2017)	Risk of reoperation (RR)	-	1.0	1.2 (CI 0.91-1.1)	0.2

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.7 Hospital length of stay.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Carlson (2017)	Mean length of stay (days)	6.2 (SD ±3.1)	8.9 (SD ±7.0)	-	*<0.01*
Baba (2013)	Mean hospitalization period (days)	29.9 (14-50; SD ±**4**)	-	29.3 (17-58; SD ±**10.25**)	NA
Bush (2007)	Average length of stay (days)	7.28 (SD ±3.98)	-	6.41 (SD ±3.52)	*0.0215*
Langlois (2015)	Length of stay (days)	10 (SD ±3,3)	-	8.7 (SD ±4.0)	0.4
Pala (2016)	Time of hospitalization (days)	12 (7-32; SD ±**6.25**)	-	14 (5-32; SD ±**6,75**)	*0,09*
Tsukada (2010)	Length of hospitalization (days)	35.4 (SD ±17,4)	-	36.1 (SD ±21,0)	0,39
Parker (2015)	Mean hospital stay (days)	-	20,3	18,5	0,4

Italic font indicates statistical significance (p < .05). Numbers derived and calculated from article data are indicated in bold. AA, anterior approach; LA, lateral approach; PA, posterior approach; SD, standard deviation; ns, not significant; NA, not available.

Appendix table B.8 Pain.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	Postoperative pain as rated by a VAS (0-10)			-	
	12h	5.6	5.5		
	24h	4.9	4.5		
	48h	4.0	3.1		
	72h	3.3	2.7		
	96h	2.9	2.0		*0.024*
Renken (2012)	Pain VAS			-	
	Day 1 postop (range)	4 (1-8) SD±1.96	5 (2-8) SD±1.66		0.88
	Day 5 postop (range)	2 (0-5) SD±1.4	4 (0-5) SD±1.6		0.14
	Day 16 postop (range)	1 (0-5) SD±1.33	2 (0-4) SD±1.53		0.035
	Day 40 postop (range)	0 (0-1) SD±0.31	1 (0-2) SD±0.82		*0.0004*
Langlois (2015)	Mean pain VAS (0-10) on fifth postoperative day	2.5 (SD ±1.4)	-	2.8 (SD ±1,3)	0.7
	Mean use of any analgesic medication related to hip pain (days)	19	-	22	1.0
	Global pain at latest follow-up (n)	8/38	-	13/44	0.5
Pala (2016)	Postoperative pain (mean NRS score 0-10 of first and second postoperative day)	2.1	-	1.5	*0.0011*
Mukka (2016)	Pain NRS (0-10) at one-year follow-up	-	2.1 (SD ±2.2)	2.0 (SD ±1.7)	ns
Leonardsson (2016)	Patients estimated the average pain in the fracture affected hip over the previous month (VAS)	-	19	17	*0.02*
Kristensen (2017)	Mean pain VAS (0-100) from the operated hip				
	At 4 months	-	22, adj 25	20, adj 23	*0.01*
	At 12 months	-	20, adj 21	17, adj 18	*0.001*
	At 36 months	-	20, adj 20	16, adj 17	*0.02*
Sayed-Noor (2016)	Trochanteric tenderness/pressure pain threshold (using an electronic algometer)	-	89 (SD ±23)	93 (SD ±20)	0.21
	Adjusted OR for trochanteric tenderness/pressure pain threshold	-	-5.58 (-18.9 to 7.76)	1.0	0.40

Italic font indicates statistical significance ($p < .05$). AA, anterior approach; LA, lateral approach; PA, posterior approach; VAS, Visual Analogue Scale; NRS, Numeric Rating Scale; postop, postoperative; ns, not significant; adj, adjusted mean value; OR, odds ratio.

Appendix table B.9 Functionality.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Auffarth (2011)	HHS on postoperative day 10	43.6	46.0	-	NA
	HHS 6 months after the procedure	66.1	67.9	-	NA
	Trendelenburg (n)	2 (8.3%)	3 (12.5%)	-	0.4
Renken (2012)	Modified Barthel score			-	
	Day 1 postop (range)	0 (0-20) SD ±5.8	0 (0-15) SD ±5.4		0.47
	Day 5 postop (range)	20 (0-50) SD ±13.6	10 (0-5) SD ±10.2		*0.009*
	Day 16 postop (range)	25 (5-50) SD ±13.1	20 (0-45) SD ±13.9		*0.05*
	Day 40 postop (range)	42.5 (5-50) SD ±14.6	30 (5-45) SD ±11.9		*0.013*
Carlson (2017)	Feet ambulated on postop day 2	29.0	24.7	-	0.84
	Ambulatory decline at 4-6 weeks	25/52 (48,1%)	20/35 (57,1%)	-	0.41
	Ambulatory decline at 4-6 months	15/50 (26,0%)	12/34 (35,3%)	-	0.70
Baba (2013)	Unaided walking at 2 weeks	26/40	-	13/39	<*0.05*
	Unaided walking at 6 months	27/40		26/39	ns
Tsukada (2010)	Walking ability of the HSS (0-10)				
	1 month after surgery	5.3	-	4.2	
	1 year after surgery	6.3		5.2	NA
	HSS 1 month postoperative	24.2 (SD ±6.4)	-	20.2 (SD ±7.4)	*0.019*
	HSS 1 year postoperative	29.9 (SD ±7.4)	-	27.2 (SD ±7.2)	0.10
Langlois (2015)	Independent walking	50%	-	37%	0.4
	Walking ability at discharge	33/38	-	41/44	1.0
	Use of 2 crutches or walker at discharge	28/38	-w	25/44	0.5
	TUG-test <10	0/38	-	6/44	
	TUG-test 10-19	19/38	-	10/44	
	TUG-test 20-29	7/38	-	16/44	
	TUG-test >30	12/38	-	12/44	0.06
	Outcomes at latest follow-up				
	Walking ability	30/38	-	37/44	1.0
	Use of cane/walker	19/38	-	25/44	0.8

Appendix table B.9 Functionality. (continued)

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Mukka (2016)	HHS at one-year follow-up	-	71 (SD ±18)	72 (SD ±17)	ns
	WOMAC at one-year follow-up	-	79 (SD ±22)	79 (SD ±24)	ns
	Adjusted OR HHS	-	-1.67 (CI -7.87 to 4.54)	1.0	ns
	Adjusted OR WOMAC	-	-1.25 (CI -9.02 to 6.53)	1.0	ns
Sayed-Noor (2016)	Limp twelve months postoperatively	-	12/24	2/24	*0.004*
	HHS twelve months postoperatively	-	75 (SD ±18)	79 (SD ±15)	0.45
	Trendelenburg twelve months postoperatively	-	9/24	1/24	*0.02*
Kristensen (2017)	Walking problems of the EQ-5D				
	After 4 months (favours PA)		NA	NA	*<0.001*
	After 1year (favours PA)		NA	NA	*<0.001*
	After 3 years (favours PA)		NA	NA	*0.009*

Italic font indicates statistical significance ($p < .05$). AA, anterior approach; LA, lateral approach; PA, posterior approach; HHS, Harris Hip Score, TUG, Timed Up and Go test; NA, not available; ns, not significant; HSS, Hospital for Special Surgery hip rating system; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D, EuroQol-5D; postop, postoperative; SD, standard deviation; NA, not available; OR, odds ratio.

Appendix table B.10 Quality of life.

Author (year)	Outcome measure	Approach			p-value
		AA	LA	PA	
Sayed-Noor (2016)	1-year EQ-5D	-	0.16	0.09	0.4
Kristensen (2017)	Mean 4-months EQ-5D	-	0.55 adj 0.45	0.57 adj 0.47	0.2
	Mean 12-months EQ-5D	-	0.61 adj 0.55	0.64 adj 0.58	*0.01*
	Mean 36-months EQ-5D	-	0.61 adj 0.56	0.66 adj 0.60	0.08
Leonardsson (2016)	EQ-5D		0.47 (SD ±0.37)	0.52 (SD ±0.37)	*0.009* adj 0.52
	Satisfaction VAS		24 (SD ±24)	22 (SD ±23)	*0.02* adj 0.25

Italic font indicates statistical significance (p < .05). AA, anterior approach; LA, lateral approach; PA, posterior approach; adj, adjusted mean; SD, standard deviation; VAS, Visual Analogue Scale; NA, not available.

Appendix C

Methodological quality assessments

Appendix table C. 1 Methodological quality assessment the randomized studies

	Approaches	RoB 2.0, source of bias				
Author (year)		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
Auffarth (2011)	AA – LA	+	+	-	+/-	+/-
Parker (2015)	LA – PA	+	+	-	+/-	+/-
Renken (2012)	AA – LA	+	+	+	+/-	+/-

+ low risk of bias, +/- some concerns of bias, - high risk of bias

Appendix table C. 2 Methodological quality assessment of the comparative cohort studies.

Author (year)	Approaches	ROBINS-I, source of bias						
		confounding	selection of participants	classification of interventions	deviations from intended intervention	missing data	measurement of outcomes	selection of the reported result
Prospective Cohort Studies								
Baba (2013)	AA – PA	-	+	+	+	-	+/-	+/-
Enocson (2008)	LA – PA	+	+	+	+	+	+	+/-
Langlois (2015)	AA – PA	+/-	+/-	+	+	+/-	+/-	+
Mukka (2016)	LA – PA	+	+/-	+	+	+/-	+	+
Sayed-Noor (2016)	LA – PA	+	+	+	+	+	+/-	+
Svenoy (2017)		+	+/-	+	+	+	+	+/-
Tsukada (2010)	AA – PA	+	+	+	+	+/-	+	+
Retrospective Cohort Studies								
Abram (2015)	LA – PA	+/-	+	+	+	+	+	+
Biber (2012)	AA – PA	+/-	+	+	-	-	+/-	-
Bush (2007)	AA – PA	+/-	+	+	+	-	+	-
Carlson (2017)	AA – LA	+/-	+	+	+	+	+	+/-
Kristensen (2017)	LA – PA	+/-	+/-	+	+	+	+	-
Leonardsson (2016)	LA – PA	+/-	-	+	+	+	+	+
Ozan (2016)	LA – PA	+/-	+/-	+	+	+	+	+
Rogmark (2014)	LA – PA	+/-	+	+	+	+/-	+	+/-
Pala (2016)	AA – PA	+/-	-	+	+	+/-	+/-	+
Sierra (2006)	AA – LA – PA	+/-	-	+	+	+	+	+
Trinh (2015)	AA – LA – PA	+/-	+	+	+	+	+/-	+

+ low risk of bias, +/- moderate risk of bias, - serious risk of bias, -- critical risk of bias, N no information

Corrigendum

The authors regret that in Table 1, it is stated that Kristensen et al. (2017) included 18,918 posterior-approach patients and 1990 lateral approach patients.[8] However, in the original article by Kristensen et al. (2017) it is stated that 'The direct lateral approach group had 18,918 patients and the posterior approach group had 1990' (and also presented as such in Table 1 of that original article).[8] The same applies for Figure 2b. This is the only meta-analysis of our systematic review which included results by Kristensen et al. (2017).[8] The mean operation times for each approach (which is analyzed in this meta-analysis), however, are not switched around. This means that the effect-size and the direction of the effect analyzed here is correct. Additionally, the effect weight is also correct as the total amount of patients remains identical. This means that the outcome of this meta-analysis (Fig. 2b) is correct.

In all other places where Kristensen et al. (2017) is referenced (chapters 'Functionality' and 'Quality of Life' of the results, and in the Discussion), the direction of the effect is also handled correctly. The amount of patients included for each approach is not mentioned elsewhere, and of no importance in those sections of our systematic review.

Consequently, the authors conclude that the switched amount of patients per approach group in Table 1 and Figure 2b have no effect on the analyses and the conclusions of their paper. The authors would like to apologise for any inconvenience caused.

The corrections of this corrigendum have already been implemented in this thesis chapter.

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Chapter 3

Surgical outcomes of the anterior and lateral approach

van der Sijp M.P.L., Niggebrugge A.H.P., Krijnen P., van Eijk M., Achterberg W.P., Schipper I.B. Comparison of the Surgical Outcomes after Hemiarthroplasty via the Anterior or Lateral Approach: An Observational Prospective Cohort Study. *[submitted]*.

Abstract

Purpose: This observational cohort study aimed to compare the anterior or lateral approach and to compare the surgical outcomes and complications related to both approaches in patients with a femoral neck fracture treated with arthroplasty.

Methods: A prospective observational cohort study included all consecutively admitted patients with a femoral neck fracture and treated with arthroplasty. The surgical approach was based on the surgeon's personal preference. The primary outcome was the overall surgical complication rate. Secondary outcomes included the individual surgical complications and reoperations, the operation time, surgical blood loss, length of hospital stay, postoperative pain and morphine use at discharge.

Results: 77 patients (18.2%) with an anterior approach and 346 patients (81.8%) with a lateral approach were included. Patients treated with an anterior approach were on average younger, had less comorbidity, better mobility and higher ADL scores. The anterior approach was performed more often for total hip arthroplasty compared to the lateral approach. No significant differences were observed in the overall surgical complication rate (7.8% vs 8.1%; P = 0.292) and reoperation rate (1.3% vs 4.3%; P = 0.33) for the anterior and lateral approach respectively. The anterior approach had a longer median operation time (80min vs 68.5min; P = 0.003) with more surgical blood loss (250ml vs 200ml; P = 0.007), but no differences in hospital stay, pain and morphine use were observed.

Conclusion: Despite selection of patients for the anterior approach, no benefits concerning surgical complications were demonstrated compared to the lateral approach, while some limitations were observed.

Introduction

Patients with a proximal femoral fracture have a high risk of mortality, impaired functional outcomes and loss of independence.[1, 2] Besides the personal impact on these patients, the required upregulation of care and associated costs also have a major societal impact. Because immobilization in older patients is associated with severe morbidity and mortality, proximal femoral fracture surgery generally aims to allow for immediate mobilization to ensure an early start of the rehabilitation process, and maximise functional outcome [3]. Arthroplasty has the advantage of enabling early mobilization without fracture pain compared to osteosynthesis.[4] In addition, it eliminates the risk of femoral head osteonecrosis and fracture-healing related complications.[4-6] Minimising the risks for surgical complications is desirable as the adverse effects of these complications are significant. Arthroplasty, however, poses other surgical complication risks including dislocation, Bone Cement Implantation Syndrome, periprosthetic fracture and deep wound infection. Each of these complications may lead to readmissions, reoperations, complete patient immobilization until resolved, and mortality. Although there is limited literature on the effects of surgical complications on functional outcome, deterioration of the patients' rehabilitation capacity, especially in older patients, is likely.[7, 8]

The anterior approach of the proximal femur aims to spare crucial muscle tissue by using the intermuscular planes and is thought to be the least invasive of all routinely used approaches. Less muscle damage[9-12], less postoperative pain[13] and improved muscle function and postoperative gait parameters have been observed for the anterior approach in elective total hip arthroplasty (THA). Though this may suggest a faster recovery, a large review by Kyriakopoulos et al. (2018) concludes that no decisive clinically relevant benefit of the anterior approach over the other surgical approaches in elective total hip surgery has been found yet.[14, 15] A recent randomized controlled trial on fracture patients however, indicated improved early patient mobilisation and pain reduction for the anterior approach compared to the lateral approach and suggested this could be especially true for frail older patients.[4, 16] Besides preserving muscle function, the anterior approach may also be favourable for joint stability, and reduce risks for dislocations.[15, 17] In elective surgery, dislocation rates tend to be more favourable for the anterior approach compared to the lateral approach.[15] Recent meta-analyses on fracture patients, however, presented no statistically significant superiority of the anterior approach in terms of the dislocation rate, or any other surgical complications.[18, 19] Despite the above described studies regarding the anterior approach, there is limited literature on the surgical outcomes and complications of the anterior approach compared to the lateral approach.

This observational cohort study therefore aims to compare patients with a femoral neck fracture treated with arthroplasty via the anterior approach or lateral approach and to compare the surgical outcomes and complications related to both approaches.

Materials and Methods

This study was performed and reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' statement guidelines for reporting observational studies.[20]

Study Design and Setting

This study is part of the 'Hip Fracture Centre' (HFC) project that prospectively documents the treatment aspects and outcomes of all consecutive hip fracture patients admitted to the study hospital.[21] The study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and all patient data were handled in accordance with 'Good Research Practice' guidelines. No individual informed consents were acquired due to the observational nature of the study and the use of routinely collected anonymous data only. The methodology of data collection and use of the data for observational studies were approved by the institutional Medical Research Ethics Committee (protocol number 16-059 and 18-029).

Patients and treatment

All adult patients admitted between December 19th 2016 and December 1st 2019 with a radiographically demonstrated femoral neck fracture (AO type 31 B1-B3) and treated with hemi- or total hip arthroplasty using the anterior or lateral approach were eligible for these study purposes.[22] Patients with pathological fractures and concomitant traumatic injuries were excluded.

Treatment and data collection

Patients admitted to the hospital with a proximal femoral fracture were treated in accordance with the treatment guidelines for 'proximal femoral fracture in elderly patients' by the Dutch Trauma Society.[23]

Patients were operated as soon as possible after full medical assessments (including laboratory tests, physical examination and consultation by a geriatric specialist) and anaesthesiologic approval.

Both the anterior approach and lateral approaches are routinely used for hemiarthroplasty or total hip arthroplasty in the study hospital. The arthroplasty was performed with either of these approaches, and the choice of approach depended on the personal experience and preference of the surgeon on duty. The surgical procedure has been described in a previous publication.[21] The prostheses used were the 3-point-contact anchorage cemented or uncemented CCA straight stem prosthesis in a standard or lateral version combined with a short or medium hemiprosthesis head, or a bimodular head in combination with a cemented advantage cup produced by Zimmer Biomet® in case of total hip arthroplasty.

Patients who lived independently before the fall were requested to visit the outpatient clinic at 6 weeks, 3 months and 1 year after surgery for routine assessments. All other patients, and those not attending the outpatient assessment, were consulted by phone, unless this was not possible. In that case, a relative, an (in)formal caregiver or the general practitioner was contacted for information. Complications were recorded during these contact moments, in addition to any emergency department visits and readmissions. The follow-up for study purposes of the included patients ended on December 12th 2019.

Data collection

Baseline demographics were recorded in an ISO27001 and ISO9001 certified, coded database by the treating physicians during admission. The demographics included the patients' age, sex, comorbidity score (using the ASA classification[24]), fracture type (displaced or non-displaced), the surgeon's experience level (resident operating independently, resident assisted by a surgeon or a surgeon with or without assistance of a resident), type of anaesthesia (spinal or general), surgical approach (anterior or lateral approach), preoperative cognition state (using the 6CIT score), body mass index and preoperative nutritional state (using the SNAQ-score[25]). The patients' baseline performance of activities of daily living (using the Katz ADL-score) and mobility (independent, walking with an aid or no independent mobility) was assessed during admission considering the period directly before the fall.

Outcome measures

The primary outcome of this study was a composite outcome parameter, constituting complications related to the surgical procedure. This included postoperative bleeding (defined as any subsequent blood loss from the operated area), implant dislocation (defined as the dislocation of the femoral head from the acetabulum), periprosthetic fracture (defined as any radiographically confirmed new fracture formed during surgery with a fracture-plane in direct contact with the prosthesis), deep wound infection (defined using the Dutch 'National Institute for Public Health and the Environment' guideline for postoperative wound infections) and nerve damage (defined as any loss of sensory or motor functions associated with the operation area).[21]

The secondary outcomes included the incidence of each of the aforementioned individual surgical complications and reoperations (defined as at least one surgical intervention on the proximal femur or hip joint at any time after the primary surgery including interventions for deep wound infections). In addition, the operation time (skin-to-skin), surgical blood loss (in ml as estimated by the operation team), maximum postoperative pain (NRS, rated three times daily for patients without a cognitive impairment), morphine use at discharge and the length of postoperative hospital stay were compared. Blinding was not possible due to the observational nature of the study. The anticipated risk of bias was low as routine care was studied in this observational study and the selected surgical outcomes were well-defined and reasonably objective.

Statistical analyses

Demographic and clinical characteristics of the anterior and lateral approach cohorts were described using summary statistics and compared using univariate analyses to reveal potential baseline differences, which may act as confounders by indication if these characteristics are expected to influence the surgeons in their choice of approach. Categorical variables were compared with the chi-squared test if the data were sufficiently large (expected cell counts, > 5) or the Fisher's exact test if this requirement was not met. Continuous variables were compared with an unpaired t-tests for normally distributed data, and by the Mann-Whitney U test for data that was not normally distributed (Kolmogorov-Smirnov test, $P < 0.05$). Missing data were not imputed.

Outcome parameters were compared univariably between the cohorts, but correction for confounding factors was of major importance because the patients in this study are not randomized. Since the number of study participants was limited relative to the number of potential confounders, a propensity score (PS) was calculated based on all available baseline parameters. The PS was then used to adjust for differences between the two cohorts in multivariable regression analyses for all outcomes.

P-values <0.05 were considered statistically significant, and denoted in italic in all tables. All statistical analyses were performed using IBM SPSS Statistics version 25. For the study purposes, a convenience sample was used by including all patients from the prespecified inclusion period.

Results

Between December 19th 2016 and December 1st 2019, a total of 423 adult patients with a femoral neck fracture were admitted and treated with arthroplasty. The median age of the included patients was 84 years (range 53-101) and the majority were female (n=288, 68.1%). The anterior approach was used for 77 patients (18.2%) and the lateral approach for 346 (81.8%). Complete data on all baseline patient characteristics was available for 397 (93.9%) patients. In the 26 (6.1%) patients with missing data, the characteristics were on average 87.7% complete.

Statistically significant differences between the anterior and lateral approach groups were observed for age, comorbidity score, cognition, mobility, prefracture living situation and Katz ADL (Table 1). Patients treated with the anterior approach were on average younger (median 77 years versus 85 years; $P < 0.001$), with a more favourable comorbidity score (ASA I-II 51.3% vs 34.2%; P =

Table 1. Patient characteristics and treatment aspects per surgical approach.

Characteristic	**LA** **N=346 (81.8%)**	**AA** **N=77 (18.2%)**	**P-value**
Patient characteristic			
Age (median, IQR)	85 (11)	77 (18)	*<0.001*
Sex, female (n, %)	237 (68.5)	51 (66.2)	0.70
Comorbidity score (n, %)			
ASA I-II	118 (34.2)	39 (51.3)	*0.007*
ASA III-IV	228 (65.9)	38 (49.4)	
BMI (mean, range)	23.3 (28.3)	23.7 (47.0)	0.44
Malnourished (n, %)	75 (22.5)	11 (14.5)	0.12
Cognitive impairment, (n, %)	151 (43.8)	16 (20.8)	*<0.001*
Mobility (n, %)			
Independent	96 (28.1)	45 (60.0)	*<0.001*
With walking aid	148 (43.3)	19 (25.3)	
No independent mobility	98 (28.7)	11 (14.7)	
Katz ADL (n, %)			
0-2	182 (53.2)	55 (72.4)	*0.002*
3-6	160 (46.8)	21 (27.6)	
Living situation (n, %)			
Independent	218 (63.0)	65 (84.4)	*0.002*
Homecare or residential home	33 (9.5%)	3 (3.9)	
Nursing home	84 (24.3)	6 (7.8)	
Other	11 (3.2)	3 (3.9)	
Fracture type (n, %)			
Undisplaced FNF	68 (19.7)	13 (16.9)	0.58
Displaced FNF	278 (80.3)	64 (83.1)	
Treatment aspects			
Time to surgery, hours (mean, range)	27.1 (203)	25.4 (66)	0.43
Surgeons' experience (n, %)			
Resident (independent)	33 (9.5)	12 (15.6)	0.19
Resident (assisted)	162 (46.8)	38 (49.4)	
Surgeon	151 (43.6)	27 (35.1)	
Implant type (n, %)			
HA	343 (99.1)	47 (61.0)	*<0.001*
THA	3 (0.9)	30 (39.0)	
Type of anesthesia (n, %)			
General	170 (49.3)	34 (44.7)	0.70
Intrathecal	175 (50.7)	42 (53.4)	

AA anterior approach, LA lateral approach, IQR interquartile range, SD standard deviation, ASA American Society of Anesthesiologists, BMI body mass index, ADL activities of daily living, FNF femoral neck fracture, HA hemiarthroplasty, THA total hip arthroplasty, Italics indicate statistical significance ($p<0.05$).

0.007), less cognitive impairment (20.8% vs 43.8%; P < 0.001), better mobility (P < 0.001) and more independence in ADL and living (P = 0.002). Besides the prevalence of cognitive impairments, no differences were observed when analysing the hemiarthroplasty patients only (Appendix table 4).

The mean follow-up of all patients was 10 months. The surgical complication rate of all patients was 8.0% (n = 34, Table 2). No difference was observed in the incidence of surgical complications between patients treated with the anterior and the lateral approach (7.8% vs 8.1%; adjusted OR, 2.06; 95% CI 0.54-7.70; P = 0.292). Also, no difference between the anterior and lateral approach was found for the incidence of the separate surgical complications (Table 2). Only nerve damage seemed more common after the anterior approach in the univariate comparison (3.9 vs 0.3%; P = 0.020), which was no longer statistically significant after adjustment for confounders (adjusted OR, 0.73; 95% CI, 0.02-24.12; P = 0.86). One patient (1.3%) treated with an anterior approach was reoperated, compared to 15 patients (4.3%) with a lateral approach (adjusted P = 0.33; Table 2). The difference in mortality 1 year after surgery was 10.8%, which was not statistically significant after adjustment for potential confounders.

Table 2. Surgical complications per surgical approach.

Complication	LA	AA	p-value	Adj OR	Adj p-value
Surgical complications	28 (8.1)	6 (7.8)	0.93	2.04 (0.54-7.70)	0.29
Nerve damage	1 (0.3)	3 (3.9)	*0.020* [a]	0.73 (0.02-24.12)	0.86
Postoperative bleeding	9 (2.6)	0 (0.0)	0.38 [a]	NA	NA
Deep wound infection	13 (3.8)	1 (1.3)	0.48 [a]	2.31 (0.22-23.86)	0.48
Implant dislocation	3 (0.9)	2 (2.6)	0.23 [a]	1.70 (0.13-22.61)	0.69
Periprosthetic fracture	5 (1.4)	2 (2.6)	0.62 [a]	0.32 (0.04-2.76)	0.30
Reoperation	15 (4.3)	1 (1.3)	0.33 [a]	3.19 (0.31-33.23)	0.33

AA anterior approach, LA lateral approach, Adj adjusted for propensity score, [a] Fisher's exact test, NA not available, *italics* indicate statistical significance (p<0.05).

The duration of surgery was significantly longer for the anterior approach compared to the lateral approach, also after adjustment with the PS, by an estimated 8 minutes (difference, -8.36; 95% CI, -13.94,-2.79; P = 0.003; Table 3). The estimated surgical blood loss was available from 280 (61.5%) patients. Significantly less surgical blood loss was observed for the LA, estimated at 80 millilitres (difference, -80.66; 95% CI, -138.72,-22.59; P = 0.007; Table 3). Pain scores during admission were available from 328 (77.5%) patients. 90 (21.3%) patients were excluded from the analyses as pain could not be rated reliably due to severe cognitive impairment or delirium during admission. No differences were observed in the maximum postoperative pain, the postoperative length of hospital stay and the frequency of morphine use at discharge.

Table 3. Non-surgical outcomes per approach.

Outcomes	LA	AA	P-value	Adj OR/B-coef	Adj p-value
Operation time, minutes (median, IQR)	68.5 (22)	80 (36)	*<0.001*	-8.36 (-13.94;-2.79)	*0.003*
Surgical blood loss, millilitres (median, IQR)	200 (150)	250 (200)	*0.001*	-80.66 (-138.72;-22.59)	*0.007*
Length of stay, days (mean, range)	5.6 (48)	4.9 (19)	0.32	0.31 (-1.46-2.07)	0.73
NRS pain (mean, range)	3.6 (9)	3.2 (10)	0.15	0.33 (-0.28-0.94)	0.29
Morphine use at discharge (n, %)	117 (33.8)	17 (22.1)	*0.045*	1.83 (0.88-3.79)	0.11
Mortality	96 (27.7)	13 (16.9)	*0.049*	1.11 (0.53-2.36)	0.78

AA anterior approach, LA lateral approach, Adj adjusted for propensity score, OR odds ratio, B-coef regression coefficient, IQR interquartile range, SD standard deviation, NRS numeric rating scale (0-10), *italics* indicate statistical significance ($p<0.05$).

When comparing the outcomes of just the hemiarthroplasty patients, no differences were observed in any of the surgical complications (adjusted OR, 2.74; 95% CI, 0.07->99.99; P=0.74; Appendix table 5).

Discussion

Significant differences in the baseline characteristics of patients treated with the anterior and lateral approach were observed in this observational cohort. Patients treated with an anterior approach were on average younger, had less comorbidity, better mobility and higher ADL scores. The anterior approach was performed far more often for a total hip arthroplasty compared to the lateral approach, which likely explains these differences in baseline characteristics. Total hip arthroplasty is generally recommended for the fitter patients with a relatively unrestricted mobility.[26, 27] A selection for the AA based on the characteristics of the patients obviously has occurred.

Due to the limited evidence in recent literature, the surgeon's choice of preferred approach may depend heavily on the time required to perform the approach and the technical difficulty. The anterior approach is associated with a significant learning curve, and many resident training programs lack exposure to this technique.[4, 28, 29] In addition, a higher risk for inadequate femoral stem positioning due to a limited exposure and visibility for less experienced surgeons have been acknowledged.[4, 15] No studies have been performed on the factors influencing surgeon's choice of surgical approach, but the overall consensus in literature is to use the approach one is most familiar with.

For total hip arthroplasty, however, surgeons may have been sufficiently motivated to use the anterior approach, by studies indicating that the less invasive anterior approach reduces the relatively high dislocation risk of total hip arthroplasty.[30-32] The additional technical difficulty of the anterior approach does not seem to outweigh the benefits of the less invasive approach for hemiarthroplasty in patients with a proximal femoral fracture yet. This may be the result of the fact that the potential benefits of the anterior approach, including reduced complication rates and improved functional outcomes, are as of yet marginally studied in hip fracture patients compared to elective hip surgery. The overall consensus in previous literature tends to be to use the approach one is most familiar with.[33-35]

No statistically significant differences between the anterior approach and the lateral approach were observed in the incidences of surgical complications and reoperations in this study. The same was true when analysing the patients treated with HA only. The overall incidence of surgical complications was 7.8% and 8.1% for the anterior and lateral approach respectively, and 1.3% compared to 4.3% for reoperations. In previous studies, incidences vary, with surgical complication rates for the anterior approach of up to 20.3% and reoperation rates up to 4.3%.[18, 35-37]

The anterior approach was associated with a significantly longer operation time (8 minutes) and more blood loss (80ml), also after adjusting for all baseline factors including the type of prosthesis. While these findings may reflect the technical challenge of the anterior approach, the observed differences seem of minor clinical relevance. A longer operation time has been reported previously by some studies, but not all.[16, 35-37] No previous studies observed less blood loss for the lateral approach compared to the anterior approach.[16, 35, 37]

Despite the fact that this study failed to find significant differences for most of the outcomes, the findings of the study add to a growing body of evidence on the topic.[16, 18, 19] Some studies have indicated modest functional benefits of the anterior approach, while no clinically relevant adverse effects are to be expected from the anterior approach. Even minor improvements in the treatment of these patients may benefit the patients' functional outcome and prevent further deterioration of their health.

Strengths and limitations

One of the strengths of this study is that it included a large population of recently treated patients with a follow-up sufficient for surgical outcomes. Due to the observational nature of the study, in which all eligible patients were included, this study population is regarded to accurately represent the general group of patients with a proximal femoral fracture who are treated with arthroplasty.

This study had a number of limitations. General limitations regarding the design, inherent to observational cohort studies, do apply. A significant difference was observed in the frequency of use of the anterior approach for hemiarthroplasty and total hip arthroplasty. This obvious correlation between the use of the anterior approach and the implantation of a total hip arthroplasty is most likely the underlying cause for the observed differences in the baseline characteristics of each cohort, and indicates confounding by indication. The absence of most baseline differences in the cohorts when analysing hemiarthroplasty patients only supports this premise (Appendix Table

A). This also explains the unbalanced number of included patients, with lateral approach patients outweighing the anterior approach patients 4-to-1.

A PS was used to adjust for all baseline differences. Because many patient characteristics relevant for the surgeons' decision to use a hemiarthroplasty or total hip arthroplasty (such as prefracture mobility, independence, cognition, severity of comorbidities and living situation) were assessed and included in the PS, the adjusted results are expected to be valid.[38]

Pain scores were only available from patients without severe cognitive impairments and may not reflect outcomes for the whole population. Because there is an undeniable diversity of experience and training among the surgeons involved in this study and elsewhere, the variation in skill and personal preferences likely adds to the generalizability of our findings.[18]

Conclusion

In this observational cohort study on patients with a proximal femoral fracture treated with arthroplasty, no demonstrable benefits were observed for the AA or LA in respect to the overall surgical complication and reoperation risks, despite selection of patients. However, limitations were observed for the AA concerning increased blood loss and a prolonged operation time compared to the LA.

Appendices

Table 4. Patient characteristics and treatment aspects per surgical approach for patients treated with a hemiarthroplasty.

Characteristic	LA N=343 (87.9%)	AA N=47 (12.1%)	P-value
Patient characteristic			
Age (median, IQR)	85 (11)	83 (17)	0.99
Sex (f) (n, %)	234 (68.2)	28 (59.6)	0.24
Comorbidity score (n, %)			
ASA I-II	116 (33.8)	14 (29.8)	0.58
ASA III-IV	227 (66.2)	33 (70.2)	
BMI (mean, range)	23.3 (28.3)	23.7 (24.1)	0.55
Malnourished (n, %)	75 (22.7)	7 (15.2)	0.25
Cognitive impairment, (n, %)	151 (44.2)	13 (27.7)	*0.032*
Mobility (n, %)			
Independent	94 (27.7)	16 (35.6)	0.48
With walking aid	148 (43.7)	19 (42.2)	
No independent mobility	97 (28.6)	10 (22.2)	
Katz ADL (n, %)			
0-2	180 (53.1)	28 (60.9)	0.32
3-6	159 (46.9)	18 (39.1)	
Living situation (n, %)			
Independent	216 (63.0)	36 (76.6)	0.24
Homecare or residential home	32 (9.3%)	3 (6.4)	
Nursing home	84 (24.5)	6 (12.8)	
Other	11 (3.2)	2 (4.3)	
Fracture type (n, %)			
Undisplaced FNF	68 (19.8)	9 (19.1)	0.91
Displaced FNF	275 (80.2)	38 (80.9)	
Treatment aspects			
Time to surgery (mean, range)	27.18 (203)	25.0 (66)	0.45
Surgeons' experience (n, %)			
Resident (independent)	32 (9.3)	8 (17.0)	0.31
Resident (assisted)	161 (46.9)	23 (48.9)	
Surgeon	150 (43.7)	16 (34.0)	
Type of anesthesia (n, %)			
General	169 (49.4)	19 (41.3)	0.30
Intrathecal	173 (50.6)	27 (58.7)	

AA anterior approach, LA lateral approach, IQR interquartile range, SD standard deviation, ASA American Society of Anesthesiologists, BMI body mass index, ADL activities of daily living, FNF femoral neck fracture, *Italics* indicate statistical significance ($p<0.05$).

Table 5. Surgical complications per surgical approach for patients treated with a hemiarthroplasty.

Characteristic	LA N (%)	AA N (%)	p-value	Adj OR	Adj p-value
Surgical complications	27 (7.9)	2 (4.3)	0.56 [a]	2.74 (0.07->99)	0.74
Nerve damage	1 (0.3)	0 (0.0)	1.00 [a]	NA	NA
Postoperative bleeding	9 (2.6)	0 (0.0)	0.61 [a]	NA	NA
Deep wound infection	13 (3.8)	1 (2.1)	1.00 [a]	2.00 (0.25-16.25)	0.52
Implant dislocation	4 (1.2)	1 (2.1)	0.48 [a]	0.45 (0.05-4.47)	0.50
Periprosthetic fracture	3 (0.9)	1 (2.1)	0.40 [a]	0.22 (0.02-2.42)	0.22
Reoperation	15 (4.5)	1 (2.1)	0.71 [a]	2.64 (0.33-21.10)	0.36
Mortality	86 (28.0)	13 (27.7)	0.96	1.14 (0.55-2.40)	0.72

AA anterior approach, LA lateral approach, Adj adjusted for propensity score, [a] Fisher's exact test, NA not available, *italics* indicate statistical significance ($p<0.05$).

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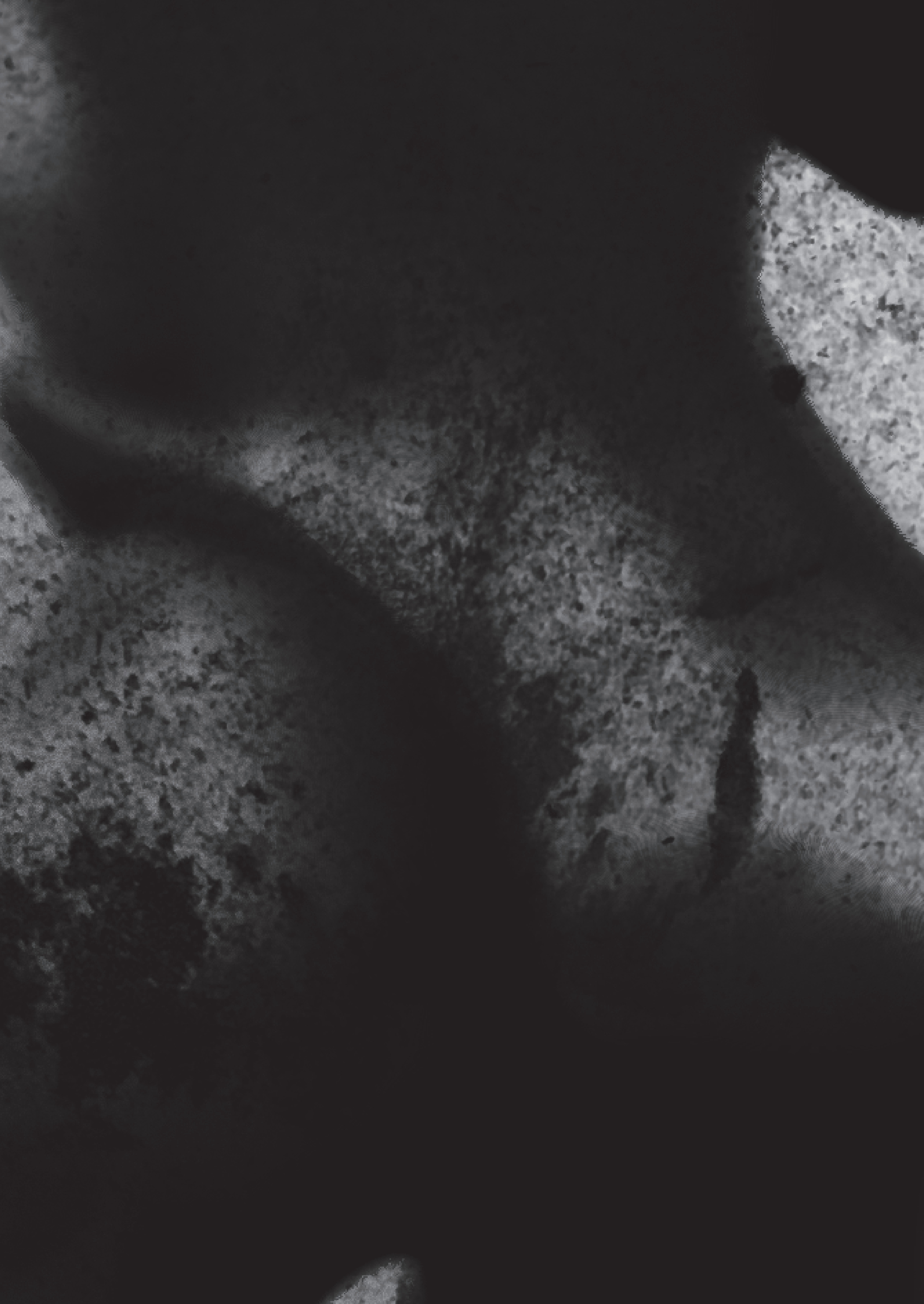
Part II

Prognostic factors of functional recovery



Chapter 4

Screening methods for malnutrition

van der Sijp M.P.L., van Eijk M., Krijnen P., Schipper I.B., Achterberg W.P., Niggebrugge A.H.P. Screening methods for malnutrition in Patients Admitted to the Hospital with A Proximal Femoral Fracture. *Injury. 2018 Dec;49(12):2239-2243*.

Abstract

Introduction: The prevalence of malnutrition in patients admitted with a proximal femoral fracture is considered high and the negative effects on health are well-studied. The SNAQ and the MNA-SF are two screening tools routinely used during admission of acute medical patients. The aim of this study is to compare the screening capacity of the SNAQ score and the MNA-SF, and to evaluate their predictive values for malnutrition using the ESPEN criteria.

Materials and methods: A single-centre study with data routinely collected prospectively from the original patient records was performed in the Haaglanden Medical Centre Bronovo in the Netherlands. All patients with a proximal femoral fracture consecutively admitted between December 19th 2016 and December 21st 2017 were included. The Intraclass Correlation Coefficient was used to assess the agreement between the malnutrition screening tools and the predictive values were calculated to compare the SNAQ with the MNA-SF using the ESPEN diagnostic criteria as the reference standard.

Results: Data was available from 437 patients. Of all patients admitted with a proximal femoral fracture 16.9% was diagnosed as malnourished by the ESPEN criteria. When screened, 20.1% (SNAQ score) to 47.8% (MNA-SF) of all patients were classified as either at risk for malnutrition or as malnourished. A moderate agreement was found between the MNA-SF and the SNAQ (κ = 0.68). The sensitivity, specificity, PPV and NPV of the SNAQ score were 71.6%, 90.4%, 60% and 94% respectively, compared to 100%, 62.8%, 35.4% and 100% for the MNA-SF.

Discussion: The SNAQ has been proven to be a very specific screening tool and the positive predictive value tends to be higher than that of the MNA-SF. However, 28.4% of all malnourished patients with a proximal femoral fracture had a negative screening test when using the SNAQ score.

Conclusions: No benefits were observed for the SNAQ over the MNA-SF as a screening tool for malnutrition in admitted patients with a proximal femoral fracture. Missing a significant portion of malnourished patients or those at risk and consequent under treatment of fragile older patients should be avoided. The well-validated MNA-SF seems more preferable as a screening tool for this patient population.

Introduction

Malnutrition can be defined as a lack of nutrition leading to diminished physical and mental function and impaired clinical outcome.[1] These negative effects of malnutrition on health are well-studied.[2] Malnutrition has been associated with delayed wound healing, increased hospital length of stay, increased risk of complications, readmissions and mortality.[2-4] Additionally, malnutrition is associated with poor functional and rehabilitation outcomes due to these impaired physical and mental capacities.[2] The prevalence of malnutrition in patients admitted with a proximal femoral fracture is considered high, but ranges widely from 6-78%, which reflects the lack of universal consensus on a definition and the diagnostic methods5. The mean age of patients with a proximal femoral fracture is above 80 years.[6] Older patients are particularly at risk of malnutrition due to the physical and metabolic changes associated with aging and morbidity, which affect long-term nutritional intake.[7] These age-related physiological changes also lead to an increased vulnerability. Many of the risk factors for malnutrition are correlated with the risk of sustaining a proximal femoral fracture.[8] In addition, hospital admission and concurrent surgical treatment of patients with a proximal femoral fracture further increases the risk of malnutrition as their regular diet is disturbed. Pre-operative fasting combined with delayed surgery can lead to deterioration of the nutritional status.[3] Postoperatively the incidence of malnutrition increases due to the patients' loss of functionality, independency and institutionalization.[7] Treatment of hospitalized patients who are malnourished or at risk for malnutrition with diets and supplements has shown to have positive effects on the complication rates, mortality and quality of life.[9-11] To improve outcome of care in the older patient with a proximal femoral fracture, early recognition and treatment of malnourishment is mandatory. Numerous screening tools are available for early detection of malnutrition.

The SNAQ (Short Nutritional Assessment Questionnaire) is the most commonly used screening tool for malnutrition during hospital admission in the Netherlands.[12] Although the effectiveness of the SNAQ as a screening tool for malnutrition in patients admitted with a proximal femoral fracture has never been validated, its use is recommended in the national treatment guidelines for the proximal femoral fracture in the older patient (2016) by the Dutch Trauma Surgery Association (NVT) and is a quality indicator for hip fracture care in the nationwide Dutch Hip Fracture Audit (DHFA).[13] In contrast, the Dutch Steering Committee 'Malnutrition' advocates the MNA-SF for older patients as part of the geriatric assessment.[14] The Mini Nutritional Assessment Short-Form (MNA-SF) is one of the most studied screening tools for both older patients and patients with a proximal femoral fracture.[5] It has been recognized by the European Society of Clinical Nutrition and Metabolism (ESPEN) as a risk screening tool to be used in combination with additional diagnostic criteria for the diagnosis of malnutrition.[1] Its use is validated for in-hospital, elderly care and community settings.[1, 15] As such it is a scientifically substantiated malnutrition screening tool for older patients[16], nonagenarians[7], acute medical patients[17] and multi-morbid patients with a proximal femoral fracture[5]. Its use has been evaluated in populations both with and without dementia.[18]

The aim of this study is to compare the screening outcomes of the SNAQ score and the MNA-SF, and to evaluate their predictive values for malnutrition using the ESPEN criteria.

Materials and methods

A single-centre cross-sectional study was performed with data that were routinely and prospectively registered simultaneously in an external database with the clinical registrations during admission and outpatient follow-ups as part of the 'Hip Fracture Centre' of the Haaglanden Medical Centre Bronovo in The Hague, the Netherlands.[19] All consecutive patients with a proximal femoral fracture (AO-classification 31A-C) admitted between December 19th 2016 and December 21st 2017 were included.

Height and weight registered on admission were used to calculate body mass index (BMI; weight (kg) / height (m)^2). Cognitive, functional and nutritional status were assessed by a trained nurse using Dutch versions of the Six-item Cognitive Impairment Test (6CIT), Katz Index of Independence in Activities of Daily Living (Katz-ADL), the MNA-SF and the SNAQ score. The patients' pre-fracture living situation was documented and the American Society of Anaesthesiologists (ASA) classification was used to assess comorbidity as part of the standard preoperative workup. Patients were considered 'cognitively impaired' if they had a known history of cognitive impairment such as dementia, if they had a 6-CIT score ≥ 11 points on admission, or if a collateral history from relatives or caregivers was necessary for adequate malnutrition assessments.

All admitted patients with a proximal femoral fracture are routinely discussed twice weekly in a multidisciplinary meeting attended by a dietician. Patients with abnormal scores or a strong clinical suspicion for malnutrition are notified to the dietician, clinically assessed and treated. Treatment or preventative measures for malnutrition with dietary strategies or nutritional supplements are only initiated when indicated.

Nutritional screening

The SNAQ score consists of three questions concerning weight loss, appetite and the use of dietary supplements (appendix A). Patients with a SNAQ score of 0 or 1 are considered 'well-nourished' and not at risk for malnourishment. Patients scoring 2 points are considered 'moderately malnourished' and patients scoring 3 points or more are considered 'severely malnourished'.[20] The MNA-SF combines five questions concerning food intake, weight loss, mobility, psychological stress or acute disease and neuropsychological problems with the BMI or (if the BMI is unavailable the) calf circumference (appendix B). 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'.[21]

A discrepancy in the three categories of the SNAQ and the MNA-SF, reflecting different parts of the nutritional spectrum is likely to exist. The common denominator of both tools, however, is the cut-off point between the normal nutritional status and an elevated risk of malnutrition (defined as ≥11 points for the MNA-SF and ≤2 points for the SNAQ); These patients, classified as having the lowest risk of malnutrition in both tools, do not require further nutritional assessments or interventions according to the specific instructions of each screening tool.[20, 21] Thus, to calculate the predictive values, the latter two high-risk groups of each tool were combined to produce binomial outcomes. For simplicity the scores above and below the aforementioned cut-off points are referred to as 'normal' and 'malnourished'. To assess the predictive values of the screening tools, the diagnostic criteria defined by ESPEN (Fig. 1) were used as the reference standard for the diagnosis malnutrition[1].

Figure 1. The ESPEN diagnostic criteria for malnutrition.

Alternative 1:
- BMI <18.5 kg/m^2

Alternative 2:
- Weight loss (unintentional) >10% indefinitely of time, or >5% over the last 3 months combined with:
    - o BMI <20 kg/m^2 if <70 years of age, or <22 kg/m^2 if ≥70 years of age
    - o FFMI <15 and 17 kg/m^2 in women and men, respectively.

BMI body mass index, FFMI fat free mass index.

Unintentional weight loss (>10% indefinitely of time or >5% over the last 3 months) was assessed using the corresponding parameter from the MNA-SF and the SNAQ score screening tools. The fat-free mass index (FFMI) was not routinely assessed and excluded from the diagnostic criteria for our study purposes.[22]

All data were handled in agreement with the 'Code of Conduct for Health Research' of the Council of the Federation of Medical Scientific Societies. Personal data was handled according to the Dutch Personal Data Protection Act. The study was approved by the institutional Medical Research Ethics Committee (METC Southwest Holland; protocol number 18-001) without the need of individual patient consent due to the observational nature of the study.

Statistical analyses

All statistical analyses were performed using IBM SPSS statistics software for Windows version 23.0. Patients without assessments of both screening tools were excluded from the analyses. Patient characteristics were described as mean and standard deviation, or number and percentage and compared using the independent sample t-test or Pearson Chi-squared test. Cross-tabulations were used to analyse the discriminative power of the screening tools, including the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The Spearman correlation coefficient (ρ) was used to assess the concurrent validity and the kappa statistic (κ) or the Intraclass Correlation Coefficient (ICC) was used to assess the agreement between the tools, interpreted as follows: 0–0.1, virtually none; 0.11–0.4, slight; 0.41–0.6, fair; 0.61–0.8, moderate; and 0.81–1, substantial.[23] P-values below 0.05 ($p < 0.05$) were considered statistically significant.

Results

A total of 485 patients with a proximal femoral fracture were admitted to the study-hospital between 19th December 2016 and 21st December 2017. Sufficient data of 437 patients (90.1%) was available. The patient characteristics are presented in Table 1. The mean age of the study population was 79.2 years (SD ±12.8) and the majority was female (69%). The mean BMI was 23.2 kg/m^2 (SD ±3.9). Cognitive impairment was present in 137 patients (31.4%). According to the ESPEN diagnostic criteria, 74 patients (16.9%) were classified as malnourished. Higher age, ASA classification and Katz-ADL score as well as cognitive impairment and living independently before the fracture were all significantly correlated with malnutrition.

Table 1. Patient characteristics of all patients and malnourished[a] patients.

Characteristics		**Total N=437 (%)**	**Malnourished (ESPEN) N=74 (16.9%)**	**Normal (ESPEN) N=363 (83.1%)**	**p-value**
Age (mean, ±SD)		79.2 (±12.8)	82.0 (±12.2)	78.6 (±12.8)	*0.037*
Gender (f)		300 (68.6)	57 (77.0)	243 (66.9)	0.088
Cognitively impaired		137 (31.4)	40 (54.1)	97 (26.7)	*<0.001*
ASA classification	I	27 (6.4)	1 (3.7)	26 (7.2)	*<0.001*
	II	188 (44.2)	20 (10.6)	168 (46.3)	
	III	188 (44.2)	42 (22.3)	146 (40.22)	
	IV	21 (4.9)	7 (33.3)	14 (3.9)	
	V	1 (0.2)	1 (2.1)	0 (0.0)	
Katz-ADL	0-1	298 (68.2)	33 (44.6)	265 (73.0)	*<0.001*
	2-5	112 (25.6)	27 (36.5)	85 (23.4)	
	6	27 (6.2)	14 (18.9)	13 (3.6)	
Living situation	Home (independent)	263 (60.2)	31 (41.9)	232 (63.9)	*0.001*
	Homecare	62 (14.2)	10 (13.5)	52 (14.3)	
	Nursing home	96 (22.0)	28 (37.8)	68 (18.7)	
	Other	16 (3.7)	5 (6.8)	11 (3.0)	
BMI (mean)		23.2 (±3.9)	18.2 (±2.2)	24.3 (±3.3)	*<0.001*
SNAQ score	≥2	88 (20.1)	53 (71.6)	35 (9.6)	*<0.001*
MNA-SF	≤11	209 (47.8)	74 (100)	135 (37.2)	*<0.001*

[a] according to the ESPEN diagnostic criteria, f Female, y Years

According to the SNAQ score 349 patients (79.9%) were classified as normal and 88 patients (20.1%) were considered malnourished; 17 (3.9%) moderately and 71 (16.2%) severely. Using to the MNA-SF, 228 of all patients (52.2%) were classified as normally nourished, 154 patients (35.2%) were at risk and 55 patients (12.6%) were malnourished (Table 2). A significant correlation was found between the SNAQ and the MNA-SF scores (ρ = -0.632, p<0.001). Agreement between the tools on classifying patients as normal and malnourished, was found for 72.4% of all patients with κ=0.68.

Table 2. Nutritional status of all femoral neck fracture patients according to the MNA-SF and SNAQ score.

MNA-SF SNAQ	Normal (14-12)	At risk (11-8)	malnourished (≤7)	Total
Well-nourished (0-1)	228 (52.2)	109 (24.9)	12 (2.7)	349 (79.9)
Moderately malnourished (2)	0 (0)	11 (2.5)	6 (1.4)	17 (3.9)
Severely malnourished (≥3)	0 (0)	34 (7.8)	37 (8.5)	71 (16.2)
Total	228 (52.2)	154 (35.2)	55 (12.6)	437 (100)

No patients were classified as malnourished by the SNAQ score and simultaneously scored as normal by the MNA-SF. Of all patients classified as normal by the SNAQ (n=349), 34.6% were classified as either at risk (n=109, 24.9%) or as malnourished (n=12, 2.7%) by the MNA-SF (Table 2). Of these 349 patients, 21 patients (6.0%) were diagnosed as malnourished using the ESPEN criteria. Of the 154 patients categorized as 'at risk' by the MNA-SF, 32 patients (20.1%) were diagnosed as malnourished using the ESPEN criteria. The PPV and NPV of the SNAQ score were 60% and 94% respectively, compared to 35.4% and 100% for the MNA-SF (Table 3).

Table 3. Predictive values of the SNAQ and MNA-SF.

	Sens	Spec	PPV	NPV
SNAQ	71.6	90.4	60.2	94.0
MNA-SF	100	62.8	35.4	100

Sens sensitivity, Spec specificity, PPV positive predictive value, NPV negative predictive value

Discussion

In our study, 16.9% of all patients admitted with a proximal femoral fracture were actually malnourished according to the ESPEN criteria. When screened, 20.1% (SNAQ score) to 47.8% (MNA-SF) of all patients were classified as either at risk for malnutrition or as malnourished. These findings are similar to those found in recent literature.[3, 24] Malnutrition was associated with age, comorbidity, cognition and reduced independence in activities of daily living and living situation.

Significant differences were observed in the prevalence of malnutrition when screening with the MNA-SF or SNAQ. Only a moderate agreement was found in the classification for malnutrition between the screening tools.

The SNAQ has been proven to be a very specific screening tool and the positive predictive value tends to be higher than that of the MNA-SF.[25] However, 28.4% of all malnourished patients with a proximal femoral fracture had a negative screening test when using the SNAQ score. The MNA-SF is a very sensitive tool, but with a poor positive predictive value. The instruments' instructions, additional criteria (such as the ESPEN criteria) or nutritional assessments by a dietician are necessary to avoid overtreatment of patients. The MNA-SF, however, seems the more appropriate tool to avoid false negative screening outcomes.[21] Treating those *at risk* of malnutrition as well as treating all older patients with a proximal femoral fracture regardless of their nutritional status has previously proven health benefits.[26] Overtreatment with non-invasive and low-cost dietary supplements seems preferable to undertreatment of the malnourished in this frail older patient population, as some studies indicate significant benefits of treating all hip fracture patients with nutritional supplements, regardless of their national status.[27]

Both screening tools assess weight loss, but the other questions of each screening tool focus on different risk factors for malnutrition. The SNAQ score is a purely anamnestic screening tool (meaning its data is obtained solely by questioning the patient), lacking objective measurements such as the BMI or FFMI. This makes it susceptible for bias when hetero anamnestic information is required in severely cognitive impaired patients, which constitutes 31.4% of this study population. In addition, age-related metabolic and behavioural changes are often associated with chronic weight loss and malnutrition, rather than acute weight loss due to recent and acute onset of disease.[28] The weight-loss questions of both the MNA-SF and the SNAQ score focus on the latter. As such, for older patients the BMI and FFMI seem more valid than anamnestic recent weight loss for the detection of malnutrition. Variations on the SNAQ score such as the 'SNAQ 65+' and 'SNAQrc' have been developed for community-dwelling older people and residential care, which respectively include the upper arm circumference and BMI as a factor.[29, 30] However, these tools are not routinely used and have not been extensively validated for hospitalized patients.

The Dutch healthcare system is advancing towards more autonomy and prolonged homestay with homecare for older people to avoid permanent institutionalization and the associated costs. This may increase the risk for malnutrition in patients with decreased self-dependence and it calls for increased awareness of healthcare professionals, adequate screening and effective treatment.

Strengths and limitations

Our study includes a large cohort of patients treated in a recent time period. Complete data were available for more than 90% of patients. Therefore, we assume the study population to be an accurate representation of patients with proximal femoral fractures.

For study purposes, we grouped the screening scores into dichotomous outcomes. As described in the results section, differences in the screening outcomes between the two tools may be attributed to the tools' inherent group discrepancies. The SNAQ score seem to make no distinction between patients are not malnourished and those who are at risk of malnourishment. The MNA-SF does, which might explain the relative overdiagnosis for malnutrition by the MNA-SF, and its poorer specificity compared to the SNAQ score.

No universal definition for malnutrition exists and many proposed definitions require labour-intensive assessments or clinical outcomes, which renders them unfit as screening tools. In this study the ESPEN diagnostic criteria were chosen as the reference standard. Use of alternative definitions and reference standards for malnutrition may give varying results when studying the effectiveness of screening tools. Future studies comparing other tools or reference standards such as the FFMI may provide additional insights into the nutritional status of this frail older patient population.

Conclusions

Based on our results, we discourage the routine use of the SNAQ score as a screening tool for older patients with a proximal femur fracture, in order to avoid missing a significant portion of malnourished patients or those at risk and consequently avoid under treatment of fragile older patients. The well-validated MNA-SF seems more preferable as a screening tool for this patient population.

Appendices

Appendix A

The SNAQ score.

Did you lose weight unintentionally?	**points**
More than 6kg in the last 6 months	3
More than 3kg in the last month	2
Did you experience a decreased appetite over the last month?	1
Did you use supplemental drinks or tube feeding over the last month?	1

Appendix B

The MNA-SF score.

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake

B Weight loss during the last 3 months
0 = weight loss greater than 3kg
1 = does not know
2 = weight loss between 1 and 3kg
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes
2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F1 Body Mass Index (BMI)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

If BMI is not available, replace question F1 with question F2. Do not answer question F2 if question F1 is already completed.

F2 Calf circumference in cm
0 = calf circumference less than 31
3 = calf circumference 31 or greater

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Chapter 5

Factors associated with functional outcome: a systematic review

van der Sijp M.P.L, van Eijk M. Tong W.H., Niggebrugge A.H.P., Schoones J. W., Blauw G.J., Achterberg W.P. Independent factors associated with long-term functional outcomes in patients with a proximal femoral fracture: A systematic review. *Exp Gerontol. 2020 Oct 1;139:111035.*

Abstract

Introduction: The current understanding of prognostic factors of functional recovery after a proximal femoral fracture is limited, and enhancements could improve the prognostic accuracy and target subgroups for additional care strategies. This systematic review aims to identify all studied factors with an independent prognostic value for the long-term functional recovery of patients with a proximal femoral fracture.

Materials and methods: Observational studies with multivariate analyses on prognostic factors of long-term functional outcome after proximal femoral fractures were obtained through an electronic search performed on November 9, 2018.

Results: In the 31 included articles, thirteen prognostic factors were studied by at least two independent studies and an additional ten by only one study. Age, comorbidity, functionality and cognition were factors for which the majority of studies indicated a significant effect. The majority of studies which included sex as a factor found no significant effect. The level of evidence for the remaining factors was deemed too low to be conclusive on their relevance for long-term functional outcome.

Conclusion: The identified factors showed overlap with prognostic factors of short-term functional outcomes and mortality. The validity and applicability of prognostic models based on these factors may be of interest for future research.

Introduction

Proximal femoral fractures in older patients are a major cause of impaired mobility, institutionalization and mortality.[1] Although the overall quality of emergency medicine, surgical procedures and post-acute care has improved in recent decades, the functional prognosis of this population is still poor.[2] The high risk for adverse outcomes coincides with the high fracture risk associated with age: a combination of acute and chronic geriatric syndromes often referred to as frailty. Adverse functional outcomes are also associated with permanent institutionalization in a nursing home and consequently have a major socioeconomic impact. Current prognostic models on the outcomes of patients with a low-energetic proximal femoral fracture show a limited accuracy, which in turn limits individualized decision-making for specific treatments and rehabilitation strategies. Insufficient prognostic accuracy and consequent reservations regarding the use of such models in clinical settings, can be attributed to the enormous heterogeneity in vitality of these patients. Constructing an accurate predictive model requires the inclusion of all relevant factors, and demands a good understanding of the mutual relationships of these factors. A recent review by Sheehan et al. identified 25 prognostic factors.[3] However, only one modifiable factor (anemia) and one immutable factor (cognition) were sufficiently substantiated by the available literature. The review included studies with short-term assessments of functional outcome (until the moment of acute care discharge) only, while functional recovery after a proximal femoral fracture is slow and may continue for up to one year after surgery.[4] Additional or different results may be expected when studying the long-term functional outcomes.

A meticulous summary of all available primary research on this topic will improve our understanding of the associations of patient characteristics and functional outcomes after a proximal femoral fracture. This systematic review aims to facilitate improvements of prognostic accuracy regarding the functional outcomes of individual patients upon admission. Better prognostic models may help to target specific patient subgroups for cost-effective additional care. This type of integrated care strategy has been shown to improve outcomes in older patients [5]. Furthermore, it may also uncover novel underlying mechanisms and mediators among previously studied factors, and thus facilitate the identification of poorly understood or poorly studied prognostic characteristics of interest for future studies. To summarize, the goal of this systematic review is to identify factors with an independent prognostic value for the long-term functional recovery of patients with a proximal femoral fracture.

Materials and methods

The study protocol was registered in the international prospective register of systematic reviews (PROSPERO, registration number 132061, 12-04-2019). The review was performed according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement guidelines.[6]

Search strategy and selection procedure

Online databases (PubMed, Embase, Web of Science, Cochrane Library, Emcare and Academic Search Premier) were searched for published studies that identified factors associated with functional recovery. Search terms were developed by a professional medical librarian (JWS) and adjusted for each database. The terms included MeSH terms and keywords for proximal femoral fractures, functional outcomes and multivariate analyses (Appendix A). The reference lists of the included articles were screened for any additional relevant articles missed by the electronic search.

All identified studies were screened by two independent reviewers (MPL, MVE) for eligibility based on the inclusion- and exclusion criteria. Any discrepancies in the article selection were resolved through discussion, when necessary, with a third reviewer (WA).

For methodological reasons, only studies on independent factors associated with long-term (6 months or longer) functional outcomes were included. The multivariate analyses had to be designed to find associations of demographics and assessments of any kind (registered during admission up to 1 week after surgery), with functional outcomes. Studies including any other factors (such as rehabilitation strategies or function later than one week after surgery) were excluded because these data are not available in the acute phase of fracture treatment and interfere with the predictive value of other variables.

As dependent variable, any assessment of functional outcome registered at or later than six months after surgery was applicable. To reduce inclusion bias, only inception cohort studies (meaning patient selection no later than the time of hospital admission for acute care) were included. Studies on absolute functional outcome were included, as well as studies on patient-specific recovery to their individual prefracture level of function. The following exclusion criteria were applied in the study selection process:

- Studies including patients with non-traumatic and elective hip surgeries.
- Studies on specific subgroups: patients with specific comorbidities, a mean age <65 years or >90 or solely inclusion of specific fracture types or causes other than low-energy traumas.
- Studies without long-term functional outcomes.
- Studies without original data.
- Meeting abstracts, editorials, commentaries, case reports and case series.
- Studies only available in languages other than English.

When two or more eligible studies reported on the same dataset, both were included if they individually presented original outcomes. If not, the methodologically most applicable one was selected.

Data extraction

The study characteristics collected from the selected articles included the first author, year of publication, study period and country, sample size, sample size (and fraction) of patients included in the multivariate analysis, design, patient inclusion- and exclusion criteria, age and sex. The extracted outcome data included the functional outcome assessment(s), the outcome stratification method (if no continuous outcome was used) and percentage of patients classified as 'successfully recovered', the type of multivariate analysis used, all prognostic factors studied, and the effect estimates. If multiple multivariate analyses were performed in the same study using different outcome assessments, stratification methods or follow-up periods, each was individually included for this review. If multiple varieties of the same multivariate analysis were presented in an article, only the most appropriate version was selected.

Outcomes

When possible, corresponding factors from different studies were grouped into the following domains: demographic (including age, sex, living situation and ethnicity), function (including functionality, cognition and psychological), biological (including comorbidity, nutritional status and vitamin D status) and treatment-related factors (including fracture type, delayed surgery and complications). An independent association between the factor and the functional outcome with a 2-sided p-value <0.05 was considered statistically significant (unless stated otherwise).

Factors included in the multivariate analysis, for which the effect was not reported (for example in stepwise regression analyses) were not assumed to have no significant effect, but were disregarded in our analyses. If a factor was studied in multiple multivariate analyses within the same study, but the effects were contradictory, the outcome was regarded as significant but mixed (and reported as such).

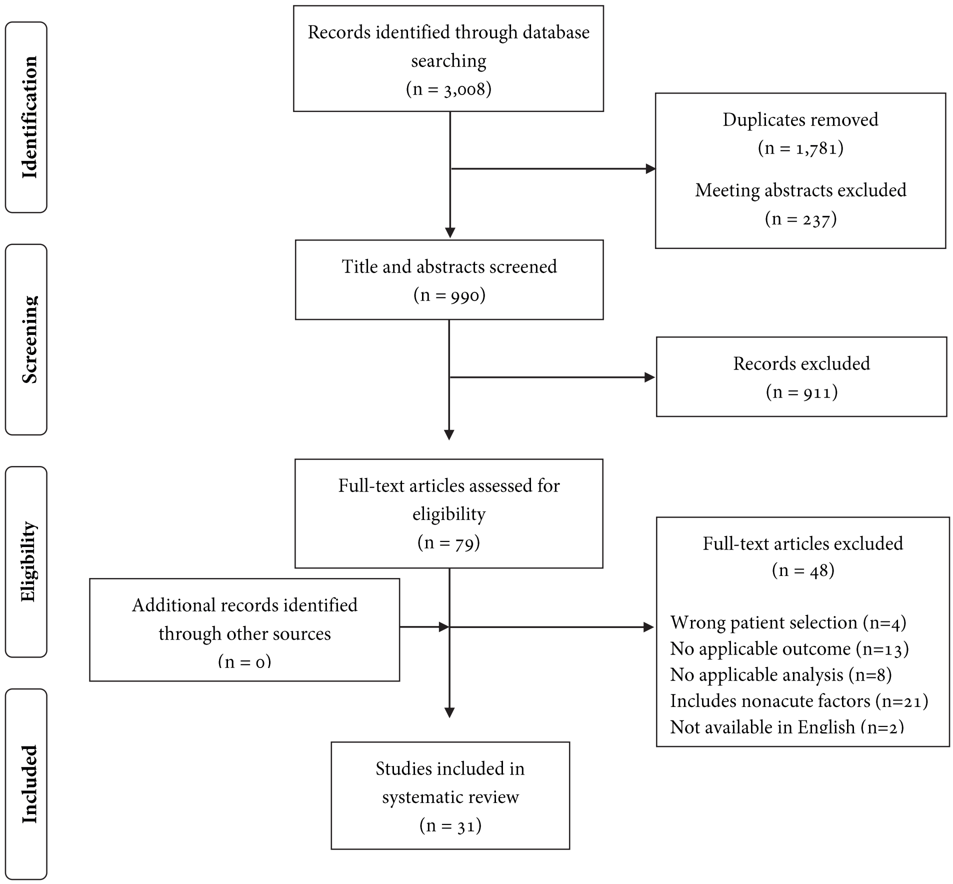
Quality assessment

The methodological quality of all included studies was independently assessed by two reviewers (MPL, WHT) using the Quality in Prognosis Studies (QUIPS) tool.[7, 8] The QUIPS tool rates the risk of bias (ROB) in six domains as either high (+), moderate (+/-) or low (-). Studies were assigned an overall high ROB if one or more domains were considered high risk. Conflicts were resolved through discussion, if necessary, with a third reviewer (MVE).

Results

A total of 3,008 references were identified. After removal of 1,781 duplicates and 237 meeting abstracts, 990 records remained. A total of 911 articles were excluded based on title and abstract, and 48 articles after full-text assessment. Predominant reasons for exclusion were no applicable functional outcomes and the inclusion of non-acute factors in the multivariate analysis (such as the type of rehabilitation program or functional assessments more than one week after discharge). A total of 31 articles were eligible for inclusion. No additional articles were obtained from the reference lists of the selected articles (Figure 1).

Figure 1. Flow diagram of the study selection process.



Study characteristics

The 31 selected studies included one cohort from a randomized controlled trial (RCT)[9] and 30 observational cohort studies, of which 26 were prospective (POC) and four retrospective (RCS).[10-13] The studies were performed between 1982 and 2018, in fourteen different countries, and included a total of 12,643 patients (range: 55[14] to 2,692[15]). Some prevalent patient exclusion criteria were high-energy traumas (HET), pathological fractures, cognitive impairments[10, 16-19], non-ambulatory status[16-18, 20-22], nursing home residence[14, 17, 18, 23, 24] or lost to follow-up (including mortality)[12, 13, 18-21, 25-28]. Most studies included older patients only, but with different lower age limits. The mean age of the patients ranged from 75[23] to 87[29], and 45%[27] to 91%[30] were female. However, not all patients included and described in each study were also included in the multivariate analysis (range: 7.9%[26] to 100%). The follow-up period varied between 6 months and 2 years after admission or surgery (Table 1).

Variance among the included studies was observed in the type of analyses performed (linear, logistic, repeated measure and cox regression analyses) and methods used (unconditionally, forward and backward conditional) (Table 2).

Fourteen studies followed the recovery of patients to their individual level of prefracture function.[9, 11, 16-18, 20-23, 25, 28, 30-32] The other studies investigated some absolute form of functional outcome, either by categorizing patients with a favorable or unfavorable outcome, or as a continuous outcome. There was considerable diversity regarding the assessment used to rate functional outcome. The most prevalent assessments used were the Functional Independence Measure score, Barthel Index (BI) and walking ability, but with various modifications. Studies with a categorical outcome used a wide variety of definitions for 'successful' and/or 'unsuccessful' recovery. The percentage of patients classified as 'successfully recovered' based on the study's own criteria ranged from 16%[19] to 87%[15]. These data were deemed too heterogeneous to pool. Some ROB was present in most studies, but eighteen studies were assigned an overall low ROB (Appendix B). Major reasons for a high ROB rating were a disproportionate number of included patients analyzed in the multivariate analysis (study attrition bias), and unknown covariates included in the multivariate analysis (study confounding bias and statistical analysis and reporting bias). The prognostic factors identified from all studies were pooled into thirteen different domains (table 3).

Prognostic factors

Demographic

Age was analyzed in nineteen studies[10-13, 15, 16, 18, 19, 21-23, 25, 26, 30-35] and was included as either a continuous or categorical factor, with large heterogeneity in the categorical cut-off values for the age groups (Appendix table D.1). Ten of the twelve studies with a low ROB found a statistically significant negative association between a favorable functional outcome and higher age (Appendix figure C.1).[10, 12, 16, 21, 23, 25, 26, 31-33] Two of these had mixed results.[15, 30] Some studies with categorized

Table 1. Characteristics of the included studies.

Author†	Year	Study period	Country‡	Sample size N (n;%) §	Design	In/exclusion criteria	Mean age (y)	Sex (%f)
Aigner 36	2017	2009-2011	DEU	402 (312; 77.6)	POC	In: ≥60y. Ex: pathologic #, polytraumas, incomplete follow-up.	81.0 (SD ±8)	72.9*
Beloosesky 10	2010	2003-2004	ISR	93 (93; 100)	RCS	In: completed follow-up. Ex: terminal illness, polytraumas, demented patients.	81.2 (SD ±7.2)	69.5
Carpintero 50	2006	2002	ESP	109 (107; 98.2)	POC	In: >65y, osteoporotic fractures. Ex: HET, pathologic #, liver/ kidney disease.	81.4 (SD ±7.2)	79.8*
Corcoles 25	2015	2005-2006	ESP	205 (165; 80.5)	POC	In: >65y. EX: dependence for ADLs, cognitive impairment, mortality.	25.4% 65-75, 48.3% 75-85, 19.5% 85-95, 6.8% >95	74.1
Cornwall 33	2004	1997-1998	USA	537 (na)	POC	In: >50y, acute fractures. Ex: bilateral #, pathologic #, concomitant injuries, previous ipsilateral #/surgery, pelvis/subtrochanteric #, operation contraindicated.	81.9 (SD ±8.9*)	81.7*
Fortinsky 14	2002	1999-2000	USA	55 (24; 43.6)	POC	In: community dwelling, ambulatory, English-speaking. Ex: polytrauma, pathologic #.	82 (SD ±6), 79c (SD ±6*)	82
Gatot 11	2016	2011-2013	SGP	153 (na)	RCS	In: complete 1y follow-up, surgical treatment.	77.0 (SD ±7.4)	67.3
Givens 9	2008	<1997*	USA	126 (na)	RCT	In: ≥65y, surgical treatment. Ex: pathologic #, life expectancy <6m.	79 (SD ±8)	78.6
Gumieiro (1) 37	2013	2010	BRA	86 (na)	POC	In: >65y. Ex: pathologic #.	80.2 (SD ±7.3)	76.7
Gumieiro (2) 39	2013	2010	BRA	82 (82; 100)	POC	In: >65y. Ex: pathologic #, pressure ulcers before admission.	80.4 (SD ±7.3)	75.6
Gumieiro 38	2015	2011	BRA	86 (na)	POC	In: ≥65y, EX: pathologic #, conservative treatment.	80.2 (SD ±7.3)	76.7*
Hannan 26	2001	1997-1998	USA	571 (45; 7.9)	POC	Ex: <50y, inpatient #, transferred patients, concurrent #/injury, pathologic #, subtrochanteric #, bilateral #, prior ipsilateral #/ surgery, mortality.	18.6% <75, 38.2% 75-84, 43.3% ≥85	81.4
Helminen 20	2017	2011-2014	FIN	594 (154; 25.9)	POC	Ex: pathologic #, periprosthetic #, prefracture inability to walk, mortality.	85 (range 65-100)*	71.5*

Table 1. Characteristics of the included studies. (continued)

Author†	Year	Study period	Country‡	Sample size N (n;%) §	Design	In/exclusion criteria	Mean age (y)	Sex (%f)
Iaboni 16	2017	2008-2012	CAN	477 (na)	POC	In: ≥60y, surgical treatment. Ex: non-ambulatory, cognitive impaired, pathologic #, interferon treatment, sensory impairment, non-English.	78.4 (SD ±8.8*)	75.5*
Ingemarsson 19	2003	-	SWE	157 (57; 36.3)	POC	Ex: severe illness, severe dementia, mortality.	80.9 (SD ±9.5)	70.7
Kim 23	2012	2005-2009	KOR	415 (415; 100)	POC	In: >60y, noninstitutionalized, LET, surgically treated, no previous #. Ex: pathologic #	75.13 (SD ±9.32)	68.2
Koval (1) 17	1998	1987-1995	USA	631 (531; 84.2)	POC	In: ≥65y, ambulatory and home dwelling, nonpathological #. Ex: moderate/severe dementia, medically predetermined anesthetic technique.	79.6 (SD na)	80.0
Koval (2) 18	1998	1988-1990	USA	398 (310*; 77.9)	POC	In: ≥65y, acute fracture, nonpathological, no severe dementia, ambulatory and home dwelling. Ex: mortality/loss to follow-up	27% ≥85	79
Lin 27	2004	2000-2001	TWN	103 (61; 59.2)	POC	In: >65y. Ex: pathologic #, mortality/loss to follow-up.	78.3 (SD ±5.8)	45.6
Marottoli 35	1992	1982-1988	USA	62 (45- 83)	POC	In: ≥65y, non-institutionalized. Ex: Insufficient data	78.2* (SD na)	72.0*
Moerman 31	2018	2008-2009	NLD	480 (364; 75.8)	POC	In: >50y. Ex: HET, pathologic #, conservative treatment.	82.6 (range 50-101)	71
Osnes 12	2004	1996-1997	NOR	593 (420; 70.8)	RCS	In: ≥50y. Ex: pathologic #, mortality.	79.8 (range 50.2-101.4)	79.3
Pajulammi 21	2015	2007-2012	FIN	611 (611; 100)	POC	In: >=65y, first #. Ex: pathologic #, periprosthetic #, prefracture inability to walk, mortality.	83*	78.4*
Pareja 29	2017	2014-2015	ESP	130 (na)	POC	In: >75y, osteoporotic #. Ex: pathologic #, HET, iron deposit disorders, intolerant to ferro therapy.	87 (IIC 83-91)	81
Penrod 15	2008	1987-2001	USA	2692 (2012-2041)	POC	In: ≥50y.	20.0% <75; 43.0% 75-84; 37.0% ≥85	78.9
Pioli 30	2016	2008-2009	ITA	774 (604; 78.0)	POC	In: ≥75y, fragility #, mobile outdoors/indoors/with help. Ex: pathologic #, major trauma.	85.8 (SD ±5.5*)	90.8*

Table 1. Characteristics of the included studies. (continued)

Author†	Year	Study period	Country‡	Sample size N (n;%) §	Design	In/exclusion criteria	Mean age (y)	Sex (%f)
Savino 22	2013	2008-2009	ITA	504 (437; 86.7)	POC	In: ≥70y, fragility #, walk independently, surgically treated. Ex: pathologic #, major trauma, previous ipsilateral #.	85.3 (SD ±5.5)	76.1
Tarazona 13	2015	2004-2008	ESP	1258 (na)	RCS	In: >69y. Ex: pathologic #, life expectancy <6m, mortality.	83.8 (SD ±6.0)	76.2
Vergara 32	2014	-	ESP	557 (557; 100)	POC	In: ≥65y. Ex: severe impairments, syncope, pathologic #, loss to follow-up.	83.2 (SD ±7.2)	84.4*
Jones 34	2017	-	CAN	383 (na)	POC	In: ≥65y. Ex: pathologic #, refractures within 5y, HET, non-English, conservative treatment.	81.3 (SD ±7.3*)	70.0*
Shyu 28	2010	2002-2005	TWN	155 (119; 76.7)	POC	In: ≥60y, surgical treatment, no cognitive impairment. Ex: mortality/loss to follow-up.	77.9 (SD ±7.78)	68.4

* Calculated or derived from article data. † multiple articles with the same first author and published in the same year are distinguished with a number between brackets. ‡ ISO 3166-1 alpha-3 country codes, § number of patients described (number of patients included for the analysis; percentage of patients included in the analysis), y years of age, f female, POC prospective observational cohort study, RCS retrospective cohort study, RCT randomized controlled trial, In inclusion criteria, Ex exclusion criteria, # fractures, HET high energy trauma, c Patients included in the multivariate analysis only,

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies.

Article author and year*	Functional assessment	Outcome stratification	Successful recovery (%)	Follow-up (mo)	Statistical analysis	Factors†
Functional recovery						
Corcoles 2015	BI	Regain of prefracture BI score	48	12	MLoR (stepwise)	Age, residence, no complications during admission, (unknown)
Gatot 2016	Montebello Rehabilitation Factor Score	RFG ≥0.5	NA	12	MLoR	Age-group, arthritis, hypercholesterolemia
Givens 2008 (1.1)	Katz ADL	≤1 point decline	47	6 (or last FU)	MLoR	Depressive symptoms / cognitive impairment / delirium / cognitive and mood disorders combined; (age, sex, ethnicity, intervention status, number of comorbidities)
Givens 2008 (1.2)	Ambulatory status	Regained ability to walk 15ft	28			
Helminen 2017 (1.1)	Mobility	Unchanged vs impaired	80	12	MLoR	MNA-SF; (age, sex, ASA, # type)
Helminen 2017 (1.2)						MNA-LF; (age, sex, ASA, # type)
Helminen 2017 (1.3)						Albumin; (age, sex, ASA, # type)
Iaboni 2017	FRS	Recovery to ≥95% of prefracture score	49	12	CPH	Use of PIM / age / ethnicity / CIRS-G score / pain / FRS; (sex, marital status, ethnicity, education, MADRS, SBT score, smoking status, drinking status, social support, number of medications)
Kim 2012	Kitamura's classification (modified)	Recovered to prefracture ability	39	24	CPH (stepwise)	Age, delay in surgery, cancer, operation type, previous #, # type
Koval 1998 (1.11)	Ambulatory status	Recovered to prefracture ability	38	6	MLoR (stepwise)	Anesthesia type, (unknown)
Koval 1998 (1.12)			47	12		Anesthesia type, (unknown)
Koval 1998 (1.21)	FRS		86	6		Anesthesia type, (unknown)
Koval 1998 (1.22)			86	12		Anesthesia type, (unknown)

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies. (continued)

Article author and year*	Functional assessment	Outcome stratification	Successful recovery (%)	Follow-up (mo)	Statistical analysis	Factors†
Koval 1998 (2.11)	Katz ADL subscale	Recovered to prefracture score	71	6	MLoR (stepwise)	Age, ASA, no comorbidities, # type, dependence in less than one IADL, dependent in no basic ADL, lived with spouse, no previous hip #
Koval 1998 (2.12)			73	12		Age, independent living, ASA, (unknown)
Koval 1998 (2.21)	Adapted IADL		42	6		Instrumental activities of daily living, ASA, (unknown)
Koval 1998 (2.22)			48	12		Age, instrumental activities of daily living independence, (unknown)
Moerman 2018	Groningen Activity Restriction Scale	Recovered IADL (GARS)	29	12	MLoR	Age, ASA, living situation, walking aids, anesthesia type, length of hospital stay, complications, prefracture IADL
Pajulammi 2015	Mobility	Same/improved mobility vs decreased	62	12	MLoR	Age, sex, BMI, ASA, memory disorder, mobility level, living arrangement, # type, time to surgery, catheter removed
Pioli 2016 (1.1)	Walking recovery	Recovered outdoor walking ability	44	6	MLoR	Age, sex, cognitive impairment, CCI, APS, ADL, IADL, Walking device, albumin at admission, delirium, surgery <48h
Pioli 2016 (1.2)			47			
Pioli 2016 (1.3)			67			
Savino 2013	Persistent walking	Recovered walking independently	NA	12	MLoR	Age / sex / HGS / cognitive impairment / depressive symptoms / BADL / caregiver assistance / CCI / vitamin D / time to surgery / early rehabilitation; (age, sex, medical center, pre-admission BADL, cognitive decline, and depressive symptoms, CCI, caregiver assistance, time before surgery, type of surgery, early rehabilitation, vitamin D)

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies. (continued)

Article author and year*	Functional assessment	Outcome stratification	Successful recovery (%)	Follow-up (mo)	Statistical analysis	Factors†
Vergara 2014 (1.1)	BI	≥90 points and no decrease >10%	29	6	MLoR	Age, sex, cerebrovascular disease, SF-12 PCS, SF-12 MCS, LCF of womac, living status
Vergara 2014 (1.2)	IADL	≥5 and no pre-post Δ-score of ≥2 points.	25			Age, sex, SF-12 MCS, LCF of womac, living status
Vergara 2014 (1.3)	BI and IADL combined		NA			Age, sex, SF-12 MCS, LCF of womac, living status
Shyu 2010 (1.1)	BI subscale	Recovered to prefracture score	73	6	GEE	Follow-up medical services / caregiving related healthcare information / social services / support group; (postdischarge period, self-care ability, length of hospital stay, concomitant diseases)
Shyu 2010 (1.2)	IADL	Recovered to prefracture score	29			
Shyu 2010 (1.3)	BI	Recovered to prefracture score	50			
Functional outcome (absolute)						
Aigner 2017 (1.11)	BI	Continuous	-	6	MLiR	Hospitalization within 3m before #; (age, Sex, ASA)
Aigner 2017 (1.12)				12		
Aigner 2017 (1.21)	TT	Continuous	-	6		
Aigner 2017 (1.22)				12		
Beloosesky 2010	FIM self-care and motor subscale	Continuous	-	6	MLiR (stepwise)	Sex, age, cognitive state, DASH, FIM, HGS
Carpintero 2006	Functional level categories	Able to walk vs unable to walk	17	12	MLoR	1,25-dihydroxycholecalciferol, 25-hydroxycholecalciferol; (unknown)
Cornwall 2004 (1.1)	FIM score	Continuous	-	6	MLiR	Age, # type, preinjury FIM; (unknown)
Cornwall 2004 (1.2)	FIM locomotion subscale					Age, preinjury FIM, preinjury locomotion FIM, # type; (unknown)

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies. (continued)

Article author and year*	**Functional assessment**	**Outcome stratification**	**Successful recovery (%)**	**Follow-up (mo)**	**Statistical analysis**	**Factors†**
Cornwall 2004 (1.3)	FIM transfer subscale					Age, preinjury FIM , # type; (unknown)
Cornwall 2004 (1.4)	FIM self-care subscale					Age, preinjury FIM , # type; (unknown)
Fortinsky 2002	FIM lower body subscale	Recovered to prefracture scores	33	6	MLoR	Rehabilitation therapy self-efficacy, prefracture locomotion, depressive symptoms
Gumieiro 2013 (1.1)	Gait status	Ambulators vs non-ambulators	70	6 (or last FU)	MLoR	NRS 2002; (age, sex, time to surgery, CRP)
Gumieiro 2013 (1.2)						ASA; (age, sex, time to surgery, CRP)
Gumieiro 2013 (1.3)						MNA; (age, sex, time to surgery, CRP)
Gumieiro 2013 (2.1)	Gait status	Ambulators vs non-ambulators	70	6 (or last FU)	MLoR	225 kDa homodimer pro-MMP 9; (age, sex, length of hospital stay, CRP)
Gumieiro 2013 (2.2)						130 kDa pro-MMP 9 +NGAL; (age, sex, length of hospital stay, CRP)
Gumieiro 2013 (2.3)						92 kDa pro-MMP 9; (age, sex, length of hospital stay, CRP)
Gumieiro 2013 (2.4)						72 kDa pro-MMP 2; (age, sex, length of hospital stay, CRP)
Hannan 2001	FIM locomotion subscale	Continuous	-	6	MLiR	Age, sex, nursing home residence, paid homecare, modified RAND, modified APACHE, dementia, prefracture locomotion
Ingemarsson 2003 (1.11)	Walking ability	Good vs moderate/ poor	16	12	MLoR (stepwise)	Prefracture outdoor walking, balance TUG; (age, prefracture independent walking, prefracture walking aids indoors, prefracture walking aids outdoors, bed to chair, walking 10m independence, walking 10m self-selected speed, standing balance, HGS, peak expiratory flow, motivation)

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies. (continued)

Article author and year*	Functional assessment	Outcome stratification	Successful recovery (%)	Follow-up (mo)	Statistical analysis	Factors†
Ingemarsson 2003 (1.12)		Good vs moderate/ poor	31			
Ingemarsson 2003 (1.21)	Activity level	High vs moderate/low	17			Balance TUG; (age, prefracture outdoor walking, prefracture independent walking, prefracture walking aids indoors, prefracture walking aids outdoors, bed to chair, walking 10 meters independence, walking 10 meters, standing balance, grip strength, peak expiratory flow, BMD grams, BMD t-score, motivation)
Ingemarsson 2003 (1.22)		High vs moderate/low	29			
Jones 2017	FIM score	Continuous	-	6	LMM	Age, sex, residence, cognition, # type, chronic conditions, proxy respondent, baseline FIM
Lin 2004 (1.1)	BI	Continuous	-	12	MLiR (stepwise)	Ability to walk outdoors; (age, marital status, sex, residence, ADL, IADL, physiological function, eyesight, hearing ability, walking status, use of walking aid, history of falling down, disease and medication history)
Lin 2004 (1.2)	IADL	Continuous	-			Ability to do housework, marriage, use of walking aid; (age, sex, residence, ADL, IADL, physiological function, eyesight, hearing ability, walking status, history of falling down, disease and medication history)
Marottoli 1992	Physical function score	Continuous	-	6	MLiR	Age, baseline physical function, SPMSQ, Emotional support, CES-D
Osnes 2004 (1.1)	Ability to perform ADL	No walking aid vs walking aid or not walking	56	12 (mean, range 184–548)	MLoR	Residence / health status / site of accident / HET / previous/later #; age, sex

Table 2. Functional outcome assessments, analyses and prognostic factors of the included studies. (continued)

Article author and year*	Functional assessment	Outcome stratification	Successful recovery (%)	Follow-up (mo)	Statistical analysis	Factors†
Osnes 2004 (1.2)		Walking independently vs not independently	na			Age, sex
Osnes 2004 (1.3)		Walking outdoors vs not outdoors independently	na			Age, sex
Pareja 2017	BI	Continuous	-	6	MLiR (stepwise)	BI, cognitive impairment, supplements on discharge, social status on discharge
Penrod 2008 (1.11)	Mobility	Independent/ dependent (vs unable)	66	6	MLoR	Age / sex / ethnicity / dementia / hypertension / arrythmia / diabetes / cancer / COPD / heart failure / angina pectoris / myocardial ischemia / stroke / Parkinson; (# type, independent walking, ADL limitations, cohort, admission year)
Penrod 2008 (1.12)		Independent (vs dependent/unable)	31			
Penrod 2008 (1.21)	Katz ADL subscale	Independent in ≥1 criterium vs 0	87			
Penrod 2008 (1.22)		Independent in ≥3 criteria vs ≤2	63			
Tarazona 2015	Walking ability	Walk 5m	56	6	MLoR	Age, sex, BI, CCI, delirium, dementia

* multiple applicable multivariate analyses performed in one study are described separately and distinguished with a decimal number.
† The effects of each factor can be found in Appendix D. Factors included in the model, but with no reported effect, are placed between brackets. If a series of factors was only adjusted for a fixed set of other factors, they are separated by a forward slash (/), and separated from the fixed set of other factors by a semicolon (;).
mo months, MLiR multiple linear regression, MLoR multiple logistic regression, GEE generalized estimating equation, CPH Cox proportional hazard, LMM linear mixed model, na not available, FU follow-up moment.

age-groups found age to be a significant factor only when patient groups with wide age differences were compared.[11, 15, 30, 34]

Sex was included by eight studies with a low ROB.[12, 13, 15, 21, 22, 30, 32, 34] Two found significant associations, although one was mixed (Appendix figure C.2).[22, 30] Whereas Savino et al. found male sex to be associated with a worse functional outcome (OR 0.50, 95% CI 0.27-0.92; p=s), the opposite was reported by Pioli et al. (for patients with a prefracture outdoor mobility only, HR 2.59, 95% CI 1.18–5.65; p=0.017) (Appendix table D.2).

Seven low ROB studies included premorbid residence[12, 21, 31, 34], caregiver support[22, 32], or discharge location[29] (Appendix table D.3). One study found no significant associations[31], and one found positive associations (with social support and living with relatives in some of the analyses)[32]. The other five studies reported an association between a more dependent form of living and worse functional outcomes (Appendix figure C.3).

Ethnicity was included by two low ROB studies (Appendix table D.4).[15, 16] Only one indicated a significant association between non-Caucasian ethnicity and a worse functional outcome (Appendix figure C.4).[16]

Function

Seventeen studies included prefracture function.[10, 13, 14, 16, 18, 19, 21, 22, 26, 27, 29-35] Many different assessments and variations thereof were used to assess prefracture functionality. These included the Katz ADL[30], BI[22, 27, 29], IADL[27, 30, 31], FIM scores[14, 33, 34], the Disabilities of the Arm, Shoulder and Hand (DASH)[10], the Physical component score of the 12-Item Short Form Survey (PCS SF-12)[32], Western Ontario and McMaster Universities Arthritis Index (WOMAC)[32] and various assessments of mobility (Appendix table D.5).[19, 21, 27, 31] Of the ten low ROB studies, those by Pioli et al. (which grouped patients according to their prefracture mobility before the analyses) and Vegara et al. had mixed outcomes.[30, 32] Eight other studies found significant positive associations between favorable prefracture functionality and favorable functional outcomes (Appendix figure C.5a).

Two studies included an assessment of functionality registered after surgery, at the moment of hospital discharge.[10, 19] Only one had a low ROB and found a significant (positive) association with better postoperative FIM scores and Handgrip Strength (HGS) (Appendix figure C.5b).[10]

Psychological status, rating depressive symptoms, was included in three studies with a low ROB (Appendix table D.6).[9, 22, 32] Only one study found a significant association, with worse functional outcome (Appendix figure C.6).[32] A similar effect was observed by Givens et al., albeit borderline significant, which may have been due to an underpowered analysis.

Cognition was rated using a wide array of assessments. Both continuous and categorical scores were used for different diagnostic tools, including the Mini–Mental State Examination test (MMSE)[9, 34], Short Portable Mental Status Questionnaire (SPMSQ)[22, 30, 35], Blessed Dementia Rating Scale (BDRS)[9], Global Deterioration Scale (GDS)[13, 29] and previously diagnosed disorders (dementia[15, 26] and memory disorders[21]) (Appendix table D.7). Of the eight studies with a low

ROB[9, 13, 15, 21, 22, 29, 30, 34], six found significant negative associations of cognition with functional outcomes, of which one had mixed outcomes[30] and two studies showed no significant associations[9, 22] (Appendix figure C.7).

Biological

Eleven studies included an assessment of general health or a comorbidity score, and an additional six studies included semi-specific comorbidities only. Validated tools or variants thereof included the Acute Physiology, Age, Chronic Health Evaluation score (APACHE)[26, 30], American Society of Anesthesiologists (ASA) Classification[18, 36, 37], Cumulative Illness Rating Scale – Geriatric (CIRS-G)[16], (modified) RAND score[26] and Charlson Comorbidity Index (CCI)[13, 22, 30]. Some studies used less conventional methods[12, 18, 34] or specific comorbidities only[11, 15, 32] (Appendix table D.8). Six low ROB studies that included general health or comorbidity assessments showed a significant association[12, 16, 30, 31, 34, 36] of which one was mixed[30] (Appendix figure C.8).

Assessments of nutritional status were included in five studies using the Nutrition Risk Screening (NRS)[37], Mini Nutritional Assessment (MNA)[20, 37], albumin levels[20, 30], Body Mass Index (BMI)[21] and 'treatment with nutritional supplements at discharge'[29] (Appendix table D.9). Two low ROB studies found a significant association between poor nutritional status and a worse functional outcome (Appendix figure C.9).[30, 37]

Vitamin D was included as a factor by three studies with a low ROB. One found a significant association with unfavorable functional outcomes[22], one reported mixed outcomes[30] and one observed no association[38] (Appendix figure C.10, Appendix table D.10).

Treatment

The fracture type was included by five studies of which three had a low ROB (Appendix table D.11).[18, 21, 23, 33, 34] Of these, only Jones et al. reported that femoral neck fractures are more favorable than per- and subtrochanteric fractures (Appendix figure C.11).

A delay in surgery defined as more than two days, was included by three studies (Appendix table D12), none of which found a significant association (Appendix figure C.12).[22, 23, 30]

Five studies examined complications. Two included all complications pooled[25, 31] and three at delirium during admission[9, 13, 30] (Appendix table D.13). Of the three studies with a low ROB, only Moerman et al. (postoperative complications pooled) found a significant negative association with functional outcome.[31] The other two, studying delirium, found no significant association (Appendix figure C.13).

Additional significantly associated factors which were included in only one study (and which didn't fit any of the previous domains), were length of hospital stay[31], serum metalloproteinases 72 kDa (pro-MMP 2)[39], use of 'potentially inappropriate medication (PIM)'[16], postoperative pain[16], site of the accident (outdoors versus indoors)[12] and whether the urinary catheter was removed during the hospital stay[21] (Appendix table D.14).

Table 3. Overview of the associations of study factors with functional outcome.

Study author (year)	Demographic				Function			Biological			Treatment		
	Age (high)	Sex (male)	Residence and social	Ethnicity (non-Caucasian)	Functionality (good)	Psychological	Cognition (poor)	Comorbidity (poor)	Nutritional status (poor)	Vitamin D (poor)	Fracture type	Delay in surgery	Complications
Low ROB studies													
Aigner 2017								-*					
Beloosesky 2010	-				+								
Givens 2008						-	+/-						+/-
Gumieiro 2013 (1)								+/-	-*				
Gumieiro 2013 (2)													
Gumieiro 2015										+/-			
Iaboni 2017	-			+	+			-					
Jones 2017	-*	+/-	-		+		-	-			-		
Kim 2012	-										+/-	+/-	
Moerman 2018	-		+/-		+			-					-
Osnes 2004	-	+/-	-*					-					
Pajulammi 2015	-	+/-			+		-		+/-		+/-		
Pareja 2017					+		-		+/-				
Penrod 2008	-*	+/-		+/-			-						
Pioli 2016	-*	+*			+*		-	-*	-*	-*		+/-	+/-
Savino 2013	+/-	-	-		+	+/-	+/-	+/-		-		+/-	
Tarazona 2015	+/-	+/-			+		-*	+/-					+/-
Vergara 2014	-	+/-	+*		+*	-							
High ROB studies													
Carpintero 2006										-			
Corcoles 2015	-		-										-
Cornwall 2004	-				-						+/-		
Fortinsky 2002					+/-	+/-							
Gatot 2016	-*												
Hannan 2001	-	+/-	-		-		+/-	+/-					
Helminen 2017									+/-				
Ingemarsson 2003	-				+/-*	+/-							
Koval 1998 (1)													
Koval 1998 (2)	-*		+/-		-*			-*			+/-		
Lin 2004			*-		-								
Marottoli 1992	+/-				-	-*	+/-						

Table 3. Overview of the associations of study factors with functional outcome. (continued)

Study author (year)	Demographic				Function			Biological			Treatment		
	Age (high)	Sex (male)	Residence and social	Ethnicity (non-Caucasian)	Functionality (good)	Psychological	Cognition (poor)	Comorbidity (poor)	Nutritional status (poor)	Vitamin D (poor)	Fracture type	Delay in surgery	Complications
Shyu 2010			+/-*										
Positive	0/12	1/8	1/5	1/2	10/10	0/3	0/8	0/9	0/4	0/3	0/3	0/3	0/4
No effect (ns)	2/12	6/8	1/5	1/2	0/10	1/3	2/8	3/9	2/4	1/3	2/3	3/3	3/4
Negative	10/12	1/8	3/5	0/2	0/10	2/3	6/8	6/9	2/4	2/3	1/3	0/3	1/4

+ significant positive association, +/- no significant association (no effect), - significant negative association, *mixed outcome because the factor was included in multiple multivariate analyses within the same study (see Table 2 and Appendix D). Factors with more than two categories (for instance: age <50 as a reference, and age 50-75 and >75 as tested categories) were regarded significant if at least one category had a significant effect.

Discussion

The aim of this systematic review was to identify factors associated with the long-term functional outcome of patients with a low-energetic proximal femoral fracture. Out of 31 studies included, thirteen factors (grouped into four domains) were described in at least two independent studies and an additional ten factors in only one study. Age, comorbidity, functionality and cognition were found to have a significant effect in the majority of studies. Most studies that included sex as a factor found no significant effect. The level of evidence for the remaining factors (including residence and social status, ethnicity, psychological status, nutritional status, vitamin D, ethnicity fracture type, delay in surgery and complications) was deemed too low to be conclusive regarding their relevance for long-term functional outcomes.

Considerable overlap was observed with the factors included in the short-term functional outcome studies described in a review by Sheehan et al., (2018).[3] Herein, cognition was also identified as a prognostic factor supported by a sufficient level of evidence. Prognostic factors for mortality in proximal femoral fracture patients have been examined in many more studies, and the pooling of data on this unambiguous outcome is less problematic. Comprehensive reviews by Hu et al., (2012) and Smith et al., (2014) indicated that age, comorbidity (high ASA grade and high CCI), cognitive impairment and pre-fracture functionality were relevant factors for mortality, in addition to male gender, residence in a care institution and intra-capsular proximal femoral fractures.[40, 41] The prognostic factors for short-term functional outcome, long-term functional outcome and mortality seem very comparable.

The identification of a relevant set of prognostic factors could enhance the accuracy of prognostic models based on those factors. Developing a well-validated prognostic model of functional outcome may help to select patients for cost-effective care strategies, that might include interventions in nutrition, varying the intensity and frequency of physiotherapy or anticipating and organizing care for ADL. However, an accurate prognostic model of the functional recovery of patients with a proximal femoral fracture remains elusive. No such model has been extensively validated or widely implemented for routine use. The advanced age of the patient population, and the wide variety of comorbidities and severities found in this group, makes development of a model extremely challenging. Using the factors identified in this and previous reviews is one approach to investigate and construct such a model.[3, 40, 41] A better understanding of the relationships of all independent variables and the dependent variable, with some acting as potential mediators and confounders, might also help to improve the model. These relationships are still poorly addressed in available studies.[3]

In any population-based study, age is regarded as one of the most important prognostic factors. Age itself, however, is simply a proxy for biological age. In an effort to improve prognostic value relative to chronological age, biological age can be determined using various combinations of physical and biological assessments. However, these models (often including biomarkers) have so far not been proven superior to chronological age in general population studies.[42, 43] In a more homogenous population, adequate assessment of comorbidities, their severity, and their impact on premorbid function may suffice. Interestingly, those studies that used the CCI to adjust for comorbidity found no association between age and functional outcome in at least some of the analysis performed.[13, 22, 30] However, of these studies only Pioli et al. found a significantly negative association with worse CCI.[30]

Besides the CCI, many other assessments were used to rate patients' comorbidity or general health status, indicating that little consensus exists and that comorbidity remains a poorly defined concept. The assessments used to rate comorbidity tend to overlap with other factors such as cognition, functionality and nutritional status. While comorbidities themselves may impair or interfere with a patients' rehabilitation capacity, premorbid functionality is probably a major mediator in many studies.[44-46] Extensively validated assessments of comorbidity (including the ASA, APACHE and CCI) are designed to represent the patients' mortality risk rather than the functional prognosis. However, mortality could also be categorized as failure to (functionally) recover. Some studies adopt this strategy[47], but many studies actually excluded all mortality cases, which could lead to variation in outcomes.

Prefracture functionality could be regarded as a mediator of comorbidity, but also as a construct of more fundamental biological factors such as physical fitness, which in turn might be a construct of muscle mass, muscle strength, cardiopulmonary capacity and functional impairments (neuromuscular comorbidities, joint pathology) and motivational or cognitive problems.[10, 19, 22] These individual factors are still poorly understood, and could be an interesting focus for future studies.

While the inclusion of more fundamental biological factors (such as biomarkers) may be one way to enhance prognostic accuracy, these factors often require intensive or impractical assessments and can complicate a model substantially. Alternatively, effective methods to assess more practical factors, or practical factors in more effective combinations, could also improve a prognostic model. Most studies included in this review, however, aimed to assess the relevance of one specific factor, rather than to design an effective prognostic model for routine clinical purposes. Systematic reviews evaluating clinical prediction models of mortality and function are available for patients with ischemic strokes, but not yet for proximal femoral fractures.[48] Some of these predictive models have been comprehensively externally validated, and routinely collected data such as age, sex, disease characteristics (severity, subtype) and comorbidities have consistently been identified as the most suitable predictive factors of functional outcome and mortality.[48]

Study limitations

Most studies on prognostic factors are observational, an approach that potentially opens a measured effect to the influence of confounders.[49] However, multivariate analyses can adjust for the effect of confounders.[49] Only studies that undertook multivariate analyses were included in this systematic review. Some studies may have been omitted due to the limitations in the search strategy. However, no additional studies were identified by screening the reference lists of included studies. Only studies written in English were included, but additional relevant information on this topic may be available in other languages.

A high ROB was observed for a substantial number of studies, which were consequently largely excluded from the discussions and conclusions of this review. The majority of studies gave a poor description of the routine in-hospital care and rehabilitation strategy and no relevant effect due to these potential variations was assumed.

Substantial heterogeneity was observed in the methods used to assess patient functionality and prognostic factors (such as comorbidity, cognition and nutritional status). In addition, every individual factor included in a multivariate analysis potentially influences the effect measure of every other included factor, and the studies analyzed in this review did not include a collective of identical factors. Consequently, pooled data or summary effect measures could not be synthesized.

The included studies also showed heterogeneity in patient selection. Thirteen excluded all deceased patients or those with an incomplete follow-up.[10-13, 18, 19, 21, 25-28, 32, 36] These studies focused on the long-term functional outcome of surviving patients only. However, studies that include deceased patients and regard this as an unfavorable functional outcome may be regarded as more useful for clinical prognostic purposes. Some studies excluded all cognitively impaired[10, 16-19], non-ambulatory[16-18, 20-22] and/or non-community dwelling patients[14, 17, 18, 23, 35]. This may have influenced the detectable effects of prognostic factors. No separate review after selections of these studies was performed.

Studies that focused on one or more specific prognostic factors, rather than a prognostic model, are suspect in terms of publication bias for positive outcomes.[16, 17, 36, 38, 50] Studies withholding the effects of specific or unknown factors included in their models are suspect for selective reporting.[16-20, 25, 27, 33, 36, 37, 39, 50] Studies on associations between factors and absolute functional outcome, and studies of recovery to individual prefracture levels of function were both included. No major differences were observed between the outcomes of these two types of studies.

This review can also provide assistance in the choice of appropriate tools and outcome assessments for future studies on the functional recovery of patients with a proximal femoral fracture. Selecting more widely used assessments improves the comparability of outcomes, and we plead against the use of new and unique assessments as a primary outcome, without proper validation or clear indications for new insights.

Conclusions

The 23 factors identified in the 31 included studies were evaluated for prognostic value in determining the functional recovery of patients with a proximal femoral fracture. Of these factors, only age, comorbidity, cognition and prefracture functionality were supported by a substantial level of evidence and thus relevant to prognostic models of routine care data.

Appendices

Appendix A

Search strategy and term (PubMed)

((“Hip Fractures”[majr] OR “Femoral Neck Fractures”[majr] OR “hip fracture”[ti] OR “proximal femoral fracture”[ti] OR “proximal femur fracture”[ti] OR “femoral neck fracture”[ti] OR “femur neck fracture”[ti] OR “trochanteric fracture”[ti] OR “collum fracture”[ti] OR “intertrochanteric fracture”[ti] OR “collum femoris fracture”[ti] OR “hip fractures”[ti] OR “proximal femoral fractures”[ti] OR “proximal femur fractures”[ti] OR “femoral neck fractures”[ti] OR “femur neck fractures”[ti] OR “trochanteric fractures”[ti] OR “collum fractures”[ti] OR “intertrochanteric fractures”[ti] OR “collum femoris fractures”[ti] OR ((“hip”[ti] OR “hips”[ti] OR “Femoral Neck”[ti] OR “proximal femoral”[ti] OR “proximal femur”[ti] OR “femur neck”[ti] OR “trochanteric”[ti] OR “collum”[ti] OR “intertrochanteric”[ti] OR “collum femoris”[ti]) AND (“fractures”[ti] OR “fracture”[ti] OR fractur*[ti]))) AND (“functional outcome”[ti] OR “functional outcomes”[ti] OR “Predictive”[ti] OR “prediction”[ti] OR predict*[ti] OR “Prognosis”[majr] OR “prognostic”[ti] OR “prognosis”[ti] OR “prognosticator”[ti] OR “prognosticators”[ti] OR “Risk Factors”[majr] OR “risk factors”[ti] OR “risk factor”[ti] OR “Recovery of Function”[majr] OR “recovery”[ti] OR “recover”[ti] OR “Rehabilitation”[majr] OR “rehabilitation”[ti] OR rehabilitat*[ti] OR “function”[ti] OR “functionality”[ti] OR “Activities of Daily Living”[majr] OR “daily living”[ti] OR “ambulation”[ti] OR “ambulant”[ti] OR “ambulatory”[ti] OR “mobility”[ti] OR “Walking”[majr] OR “walking”[ti] OR “dependence”[ti] OR “dependent”[ti] OR “independency”[ti] OR “independent”[ti] OR “Gait”[mesh] OR “gait”[ti] OR “Postural Balance”[mesh] OR “balance”[ti]) AND (“Multivariate Analysis”[Mesh] OR “multivariate analyses”[tw] OR “multivariate analysis”[tw] OR “Logistic Models”[Mesh] OR “logistic regression”[tw] OR “logistic regressions”[tw] OR “logistic model”[tw] OR “logit models”[tw] OR “logit model”[tw] OR “hazard ratios”[tw] OR “hazard ratio”[tw] OR “Odds Ratio”[Mesh] OR “odds ratios”[tw] OR “odds ratio”[tw] OR “odds ratios”[tw] OR “cross product ratio”[tw] OR “cross-product ratios”[tw] OR “relative odds”[tw] OR “risk ratio”[tw] OR “risk ratios”[tw] OR “Analysis of Variance”[mesh] OR “analysis of variance”[tw] OR “analyses of variance”[tw] OR “ANOVA”[tw] OR “variance analyses”[tw] OR “variance analysis”[tw]) AND (english[la] OR dutch[la])

Appendix B

Appendix table B.1. Methodological risk of bias assessment of the included studies.

Study author and year	QUIPS tool Biases						
	Study Participation	**Study Attrition**	**Prognostic Factor Measurement**	**Outcome Measurement**	**Study Confounding**	**Statistical Analysis and reporting**	**Overall**
Aigner 2017	-	-	+/-	-	+/-	+/-	Low
Beloosesky 2010	+/-	+/-	+/-	+/-	+/-	+/-	Low
Carpintero 2006	-	-	-	-	+	+/-	High
Corcoles 2015	-	-	-	-	+	+/-	High
Cornwall 2004	-	+/-	-	-	+	+	High
Fortinsky 2002	-	+	-	-	+	+	High
Gatot 2016	-	-	+/-	-	+	+/-	High
Givens 2008	+/-	-	-	-	-	-	Low
Gumieiro 2013) (1)	-	+/-	-	+/-	+/-	+/-	Low
Gumieiro 2013 (2)	-	+	-	+/-	-	-	Low
Gumieiro 2015	-	+/-	-	+/-	+/-	+/-	Low
Hannan 2001	-	+	-	+	-	+	High
Helminen 2017	-	+	-	-	+/-	+/-	High
Iaboni 2017	-	+/-	-	-	-	-	Low
Ingemarsson 2003	+	+	-	+/-	+	+	High
Jones 2017	+/-	-	-	-	-	+/-	Low
Kim 2012	-	-	-	-	-	-	Low
Koval 1998 (1)	-	-	+/-	+/-	+	+	High
Koval 1998 (2)	-	-	-	-	+	+	High
Lin 2004	-	+	+/-	+/-	+	+	High
Marottoli 1992	-	-	-	-	-	+	High
Moerman 2018	-	+/-	-	-	+/-	-	Low
Osnes 2004	-	+/-	-	-	+/-	+/-	Low
Pajulammi 2015	-	-	-	-	-	-	Low
Pareja 2017	-	+/-	+/-	+/-	+/-	+/-	Low
Penrod 2008	+/-	+/-	-	-	-	-	Low
Pioli 2016	-	+/-	-	-	-	+/-	Low
Savino 2013	-	+/-	-	-	-	-	Low
Shyu 2010	-	+/-	+/-	+/-	+	-	High
Tarazona 2015	-	+/-	-	-	-	-	Low
Vergara 2014	-	-	-	-	-	-	Low

+ high risk of bias, +/- moderate risk of bias, - low risk of bias.

Appendix C

Appendix figure C.1. The association between higher age and functional outcome.

Study	ROB	Effect: Negative	Effect: No effect (ns)	Effect: Positive
Beloosesky 2010	Low	■		
Iaboni 2017	Low	■		
Jones 2017	Low	■		
Kim 2012	Low	■		
Moerman 2018	Low	■		
Osnes 2004	Low	■		
Pajulammi 2015	Low	■		
Penrod 2008	Low	■	■	
Pioli 2016	Low	■	■	
Savino 2013	Low		■	
Tarazona 2015	Low		■	
Vegara 2014	Low	■		
Corcoles 2015	High	■		
Cornwall 2004	High	■		
Gatot 2016	High	■		
Hannan 2001	High	■		
Ingemarsson 2003	High		■	
Koval 1998 (2)	High	■	■	
Marottoli 1992	High		■	
		Negative	No effect (ns)	Positive

Appendix figure C.2. The association between male sex and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Jones 2017	Low		■	
Osnes 2014	Low		■	
Pajulammi 2015	Low		■	
Penrod 2008	Low		■	
Pioli 2016	Low		■	■
Savino 2013	Low	■		
Tarazona 2015	Low		■	
Vegara 2014	Low		■	
Hannan 2001	High		■	
		Negative	No effect (ns)	Positive

Appendix figure C.3. The association between residence or social status and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Jones 2017	Low	■		
Moerman 2018	Low		■	
Osnes 2004	Low	■	■	
Pajulammi	Low	■		
Pareja 2017	Low	■		
Savino 2013	Low	■		
Vergara 2014	Low			■
Corcolez 2015	High	■		
Hannan 2001	High	■		
Koval 1998 (2)	High		■	
Lin 2004	High	■	■	
Shyu 2010	High	■	■	■
		Negative	No effect (ns)	Positive

Appendix figure C.4. The association between ethnicity (non-Caucasian) and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Iaboni 2017	Low	■		
Penrod 2008	Low		■	
		Negative	No effect (ns)	Positive

Appendix figure C.5a. The association between good prefracture functionality and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Beloosesky 2010	Low			■
Iaboni 2017	Low			■
Jones 2017	Low			■
Moerman 2018	Low			■
Pajulammi 2015	Low			■
Pareja 2017	Low			■
Pioli 2016	Low		■	■
Savino 2013	Low			■
Tarazona 2015	Low			■
Vegara 2014	Low		■	■
Cornwall 2004	High			■
Fortinsky 2002	High		■	
Hannan 2001	High			■
Ingemarsson 2003	High			■
Koval 1998 (2)	High		■	■
Lin 2004	High			■
Marottoli 1992	High			■
		Negative	No effect (ns)	Positive

Appendix figure C.5b. The association between functionality at discharge and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Beloosesky 2010	Low			■
Ingemarsson 2003	High		■	■
		Negative	No effect (ns)	Positive

Appendix figure C.6. The association between (worse) psychological status and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Givens 2008	Low		■	
Savino 2013	Low		■	
Vergara 2014	Low	■		
Fortinsky 2002	High		■	
Ingemarsson 2003	High		■	
Marottoli 1992	High	■	■	
		Negative	No effect (ns)	Positive

Appendix figure C.7. The association between cognitive impairment and functional outcome.

Study	ROB	Effect		
		Negative	No effect (ns)	Positive
Jones 2017	Low	■		
Givens 2008	Low		■	
Pajulammi 2015	Low	■		
Pareja 2017	Low	■		
Penrod 2008	Low	■		
Pioli 2016	Low	■	■	
Savino 2013	Low		■	
Tarazona 2015	Low	■		
Hannan 2001	High		■	
Marottoli 1992	High		■	
		Negative	No effect (ns)	Positive

Appendix figure C.8. The association between comorbidity or worse health status and functional outcome.

Study	ROB	Effect: Negative	Effect: No effect (ns)	Effect: Positive
Aigner 2017	Low	■		
Gumieiro 2013 (1)	Low		■	
Iaboni 2017	Low	■		
Jones 2017	Low	■		
Moerman 2018	Low	■		
Osnes 2004	Low	■		
Pioli 2016	Low	■	■	
Savino 2013	Low		■	
Tarazona 2015	Low		■	
Hannan 2001	High		■	
Koval 1998 (2)	High	■	■	
		Negative	No effect (ns)	Positive

Appendix figure C.9. The association between poor nutritional status age and functional outcome.

Study	ROB	Effect: Negative	Effect: No effect (ns)	Effect: Positive
Gumieiro 2013 (1)	Low	■	■	
Pioli 2016	Low	■	■	
Pareja 2017	Low		■	
Pajulammi 2015	Low		■	
Helminen 2017	High	■	■	
		Negative	No effect (ns)	Positive

Appendix figure C.10. The association between vitamin D status and functional outcome.

Study	ROB	Effect: Negative	Effect: No effect (ns)	Effect: Positive
Gumieiro 2015	Low		■	
Pioli 2016	Low		■	■
Savino 2013	Low		■	
Carpentero 2006	High		■	
		Negative	No effect (ns)	Positive

Appendix figure C.11 The association between fracture type (femoral neck fracture) and functional outcome.

Study	ROB	Effect: Negative		No effect (ns)		Positive
Jones 2017	Low				■	
Kim 2012	Low			■		
Pajulammi 2015	Low			■		
Cornwall 2004	High			■		
Koval 1998 (2)	High			■		
		Negative		No effect (ns)		Positive

Appendix figure C.12. The association between a delay in surgery and functional outcome.

Study	ROB	Effect: Negative	No effect (ns)	Positive
Kim 2012	Low		■	
Pioli 2016	Low		■	
Savino 2013	Low		■	
		Negative	No effect (ns)	Positive

Appendix figure C.13. The association between complications during admission and functional outcome.

Study	ROB	Effect: Negative		No effect (ns)	Positive
Givens 2008	Low			■	
Moerman 2018	Low		■		
Pioli 2016	Low			■	
Tarazona 2015	Low			■	
Corcolez 2015	High		■		
		Negative		No effect (ns)	Positive

Appendix D

Appendix table D.1. Raw extracted data on age as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Beloosesky 2010	Age		Beta 0.134, p=0.036
Iaboni 2017	Age		Coef -0.047, Exp(Coef) 0.954, SE(Coef) 0.008, Z -5.67, pr>z 0.000
Jones 2017	Age	67-74	Ref
		75-84	Coef -2.14 (95% CI -0.41-0.14) p=0.066
		≥85	Coef -4.61 (95% CI -7.17;-2.06) p<0.001
Kim 2012	Age	≥80	HR 0.77 (95% CI 0.41-1.23) p=0.035
Moerman 2018	Age		B 0.20 beta 0.11 T 3.22 p=0.001
Osnes 2004 (1.1)	Age	50-74	Ref
		75-79	OR 2.57 (95% CI 1.43-4.65) p=s
		80-84	OR 6.02 (95% CI 3.37-10.8) p=s
		≥85	OR 11.3 (95% CI 5.94-21.5) p=s
Osnes 2004 (1.2)	Age	50-74	Ref
		75-79	OR 2.15 (95% CI 0.93-4.96) p=s
		80-84	OR 10.6 (95% CI 3.85-29.0) p=s
		≥85	OR 17.8 (95% CI 3.78-83.7) p=s
Osnes 2004 (1.3)	Age	50-74	Ref
		75-79	OR 3.59 (95% CI 1.95-6.63) p=s
		8≥5	OR 5.25 (95% CI 2.90-9.49) p=s
		≥85	OR 7.45 (95% CI 4.02-13.8) p=s
Pajulammi 2015	Age		OR 1.06 (95% CI 1.02-1.09) p=s
Penrod 2008 (1.11)	Age	<75	Ref
		75-85	OR 0.76 (95% CI 0.52-1.09) p=0.13
		≥85	OR 0.69 (95% CI 0.46-1.03) p=0.07
Penrod 2008 (1.12)	Age	<75	Ref
		75-85	OR 0.54 (95% CI 0.40-0.70) p<0.0001
		≥85	OR 0.46 (95% CI 0.40-0.70) p<0.0001
Penrod 2008 (1.21)	Age	<75	Ref
		75-85	OR 0.65 (95% CI 0.40-1.06) p=0.08
		≥85	85 OR 0.64 (95% CI 0.39-1.08) p=0.10
Penrod 2008 (1.22)	Age	<75	Ref
		75-85	OR 0.59 (95% CI 0.43-0.83) p<0.001
		≥85	OR 0.38 (95% CI 0.27-0.53) p<0.0001
Pioli 2016 (1.1)	Age	Continuous	p=0.000
	Age	<80	Ref
		80-84	HR 0.84 (95% CI 0.40-1.74) p=0.635

Appendix table D.1. Raw extracted data on age as a prognostic factor of functional outcome. (continued)

Study	Factor	Category	Coefficients, p-values
		85-89	HR 0.23 (95% CI 0.09–0.55) p=0.001
		≥90	HR 0.07 (95% CI 0.01–0.36) p=0.001
Pioli 2016 (1.2)	Age	Continuous	p=0.518
	Age	<80	Ref
		80-84	HR 1.90 (95% CI 0.71–5.09) p=0.201
		85-89	HR 1.10 (95% CI 0.40–3.06) p=0.850
		≥90	HR 1.03 (95% CI 0.37–2.84) p=0.958
Pioli 2016 (1.3)	Age	Continuous	p=0.673
	Age	<80	Ref
		80-84	HR 1.13 (95% CI 0.27–4.80) p=0.869
		85-89	HR 0.87 (95% CI 0.17–4.44) p=0.862
		≥90	HR 2.08 (95% CI 0.47–9.25) p=0.335
Savino 2013	Age		OR 0.98 (95% CI 0.93-1.03) p=ns
Tarazona 2015	Age		OR 0.971 95%CI (0.941-1.003) p=0.078
Vegara 2014 (1.1)	Age		OR 1.10 (95% CI 1.07-1.14) p<0.0001
Vegara 2014 (1.2)			OR 1.16 (95% CI 1.12-1.20) p<0.0001
Vegara 2014 (1.3)			OR 1.15 (95% CI 1.11-1.20) p<0.0001
Corcoles 2015	Age	>85	B 0.089 Exp(B) 1.093 (95% CI 1.037-1.152) p=0.001
Cornwall 2004 (1.1)	Age		p = 0.004
Cornwall 2004 (1.2)			p = 0.010
Cornwall 2004 (1.3)			p = 0.005
Cornwall 2004 (1.4)			p = 0.009
Gatot 2016	Age	60-69	Ref
		70-79	B -0.667; OR 0.513 (95% CI 0.201-1.310) p=0.163
		80-89	B -1.269; OR 0.281 (95% CI 0.100-0.790) p=0.016
		≥90	B -0.785; OR 0.456 (95% CI 0.067-3.083) p=0.421
Hannan 2001	Age		Parameter estimate -0.044, p=0.02
Ingemarsson 2003 (1.11)	Age		p=ns
Ingemarsson 2003 (1.12)			p=ns
Ingemarsson 2003 (1.21)			p=ns
Ingemarsson 2003 (1.22)			p=ns
Koval 1998 (2.11)	Age	≥85	p<0.001
Koval 1998 (2.12)			p<0.001
Koval 1998 (2.21)			p=ns
Koval 1998 (2.22)			p=0.021
Marottoli 1992	Age		Estimate -0.015 SE 0.018 p=0.399

Appendix table D.2. Raw extracted data on sex as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Jones 2017	Sex	Male	Coef -0.87 (95% CI -2.84-1.10) p=0.387
Osnes 2004 (1.1)	Sex	Male	OR 0.99 (95%CI 0.58-1.70) p=ns
Osnes 2004 (1.2)			OR 0.56 (95% CI 0.25-1.25) p=ns
Osnes 2004 (1.3)			OR 0.88 (95% CI 0.53-1.46) p=ns
Pajulammi 2015	Sex	Female	OR 0.88 (95% CI 0.55-1.38) p=ns
Penrod 2008 (1.22)			OR 1.01 (95% CI 0.76-1.34) p=0.94
Penrod 2008 (1.11)	Sex	Male	OR 1.01 (95% CI 0.76-1.44) p=0.85
Penrod 2008 (1.12)			OR 0.93 (95% CI 0.71-1.21) p=0.58
Penrod 2008 (1.21)			OR 0.94 (95% CI 0.63-1.41) p=0.77
Pioli 2016 (1.1)	Sex	Male	HR 2.59 (95% CI 1.18–5.65) p=0.017
Pioli 2016 (1.2)			HR 0.81 (95% CI 0.30–2.21) p=0.679
Pioli 2016 (1.3)			HR 0.27 (95% CI 0.06–1.30) p=0.102
Savino 2013	Sex	Male	OR 0.50 (95% CI 0.27-0.92) p=s
Tarazona 2015	Sex	Male	OR 1.088 (95% CI 0.665-1.778) p=0.737
Vegara 2014 (1.1)	Sex	Male	OR 1.09 (95% CI 0.57-2.06) p=0.801
Vegara 2014 (1.2)			OR 0.87 (95% CI 0.44-1.7) p=0.675
Vegara 2014 (1.3)			OR 1.24 (95% CI 0.60-2.59) p=0.445
Hannan 2001	Sex	Male	Parameter estimate -0.371, p=0.36

Appendix table D.3. Raw extracted data on the residence and social status as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Jones 2017	Living situation	Home (ref)	Coef -3.81 (95% CI -5.87;-1.74) p<0.001
Moerman 2018	Living situation	Independent	B 2.92 beta 0.07 T 1.77 p=0.078
Osnes 2004 (1.1)	Living situation	Alone (ref)	OR 0.91 (95% CI 0.55-1.51) p=ns
Pajulammi 2015	Living arrangement	Other than home	OR 2.14 (95% CI 1.33-3.44) p=s
Pareja 2017	Social status on discharge	Nursing home	B -6.496 (95% CI -11.172 to -1.820) p=0.007
Savino 2013	Caregiver assistance		OR 0.34 (95% CI 0.18-0.63) p=s
Vergara 2014 (1.1)	Living status	Alone	Ref
		Social support	na (p=ns)
		With relative	na (p=ns)
Vergara 2014 (1.2)		Alone	Ref
		Social support	OR 2.44 (95% CI 0.87-6.86) p=0.091
		With relative	OR 3.29 (95% CI 1.23-8.83) p=0.018
Vergara 2014 (1.3)		Alone	Ref
		Social support	OR 3.79 (95% CI 1.28-11.21) p=0.023
		With relative	OR 3.92 (95% CI 1.42-10.79) p=0.013

Appendix table D.3. Raw extracted data on the residence and social status as a prognostic factor of functional outcome. (continued)

Study	Factor	Category	Coefficients, p-values
Corcoles 2015	Residence	Own home	B -2.857 Exp(B) 0.057 (95% CI 0.007-0.483) p=0.009
Koval 1998 (2.11)	Living with spouse		na, p=ns
Koval 1998 (2.12)			na, p=ns
Koval 1998 (2.21)			na, p=ns
Koval 1998 (2.22)			na, p=ns
Hannan 2001	Dependent living	None	Ref
		Homecare	Estimate -0.602 p=0.10
		Nursing home	Estimate -1.406 p=0.02
Lin 2004 (1.1)	Marriage		p=ns
Lin 2004 (1.2)	Marriage		B -2.184 SE 0.796 Beta -0.291 R^2 0.485 p<0.0001
Shyu 2010 (1)	Follow-up medical services		OR 1.10 p=0.736
	Caregiving related healthcare information		OR 0.38 p=0.009
	Social services		OR 0.57 p=0.12
	support group		OR 1.93 p=0.027
Shyu 2010 (2)	Follow-up medical services		OR 1.05 p=0.825
	Caregiving related healthcare information		OR 1.91 p=0.058
	Social services		OR 0.40 p=0.035
	support group		OR 0.29 p=0.02
Shyu 2010 (3)	Follow-up medical services		OR 1.13 p=0.746
	Caregiving related healthcare information		OR 1.70 p=0.186
	Social services		OR 0.41 p=0.076
	support group		OR 0.96 p=0.939

Appendix table D.4. Raw extracted data on ethnicity as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Iaboni 2017	Ethnicity	Other (non-white/Caucasian)	Coef -0.755, Exp(Coef) (HR) 0.470, SE Coef 0.310, z -2.43, pr>z 0.010
Penrod 2008 (1.11)	Ethnicity	White	OR 1.54 (95% CI 1.01-2.37) p=0.05
Penrod 2008 (1.12)			OR 0.95 (95% CI 0.64-1.40) p=0.77
Penrod 2008 (1.21)			OR 1.52 (95% CI 0.89,2.62) p=0.13
Penrod 2008 (1.22)			OR 1.20 (95% Ci 0.79,1.82) p=0.40

Appendix table D.5a. Raw extracted data on prefracture function as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Pioli 2016 (1.1)	Katz ADL		HR 1.06 (95% CI 0.61–1.84) p=0.834
	Lawton-Brody IADL		HR 1.24 (95% CI 1.01–1.53) p=0.042
	Walking device		HR 0.35 (95% CI 0.15–0.83) p=0.016
Pioli 2016 (1.2)	Katz ADL		HR 1.46 (95% CI 1.07–2.00) p=0.017
	Lawton-Brody IADL		HR 1.03 (95% CI 0.82–1.29) p=0.824
	Walking device		HR 0.76 (95% CI 0.38–1.54) p=0.449
Pioli 2016 (1.3)	Katz ADL		HR 1.54 (95% CI 1.03–2.32) p=0.037
	Lawton-Brody IADL		HR 1.37 (95% CI 0.77–2.42) p=0.289
	Walking device		HR 2.42 (95% CI 0.77–7.63) p=0.130
Cornwall 2004 (1.1)	Preinjury overall FIM score		p<0.001
Cornwall 2004 (1.2)	Preinjury overall FIM score		p<0.001
Cornwall 2004 (1.3)	Preinjury overall FIM score		p<0.001
Cornwall 2004 (1.4)	Preinjury overall FIM score		p<0.001
	Preinjury locomotion FIM		p<0.001
Hannan 2001	Locomotion FIM		OR 0.498 p<0.001
Iaboni 2017	FRS		Coef -0.045, Exp(coef) 0.956, se Coef 0.009, z -4.81, pr>z 0.000
Marottoli 1992	Physical function score	(0-5)	Estimate 0.237 (SE 0.086) p=0.008
Fortinsky 2002	locomotion FIM		OR 0.66 (95% CI 0.24-1.84) p=ns
Ingemarsson 2003 (1.11)	Prefracture outdoor walking		Regression -1.38, SE 0.60, OR 0.25 (95% CI 0.08-0.81) p = 0.020
Ingemarsson 2003 (1.12)			Regression -0.39, SE 0.19, OR 0.68 (95% CI 0.47-0.98) p = 0.037
Ingemarsson 2003 (1.22)	Prefracture independent walking		Regression -2.07, SE 0.72, OR 0.13 (95% CI 0.03-0.52) p = 0.004
Pajulammi 2015	Mobility level (n, %)	Outdoors unassisted	Ref
		Outdoor assisted	OR 0.47 (95% CI 0.30–0.75) p=s
		Indoor assisted	OR 0.25 (95% CI 0.09–0.72) p=s
Beloosesky 2010	DASH scores		B 0.255 p=0.005
Moerman 2018	Prefracture use of walking aids		B 3.91 beta 0.11 T 2.39 p=0.017
	prefracture IADL (GARS)		B 0.60 beta 0.56 t 10.74 p=0.000
Koval 1998 (2.11)	IADL		p<0.001
Koval 1998 (2.12)	IADL		p=ns

Appendix table D.5a. Raw extracted data on prefracture function as a prognostic factor of functional outcome. (continued)

Study	Factor	Category	Coefficients, p-values
Koval 1998 (2.22)	IADL		p=ns
Savino 2013	BI difficulty		OR 0.42 (95% CI 0.24-0.76) p=s
	HGS	Tertiles, lowest	Ref
		Intermediate	OR 2.40 (95% CI 1.24-4.62) p=s
		Highest	OR 2.46 (95% CI 1.11-5.44) p=s
Pareja 2017	BI		B 0.596 (95% CI 0.409-0.782) p<0.001
Tarazona 2015	BI		OR 1.022 (95% CI 1.014-1.030) p<0.001
Lin 2004 (1.1)	BI	ability to walk outdoors before fracture	B 40.004, SE 7.603 Beta 0.635 R^2 0.397 F 27.65 p<0.0001
Lin 2004 (1.2)	IADL Ability to do housework		B 4.706 SE 0.796 -beta 0.291 R^2 0.485 F? p<0.0001
	Use of walking aid		B -2.400, SE 0.912 Beta -0.290 R^2 0.561 p<0.0001
Vergara 2014 (1.1)	LCF WOMAC		OR 1.36 (95% CI 1.2-1.55) p<0.0001
	SF-12 (PCS)		OR 0.69 (95% CI 0.52-0.92) p=0.010
Vergara 2014 (1.2)	LCF WOMAC		OR 1.36 (95% CI 1.23-1.51) p<0.0001
	SF-12 (PCS)		p=ns
Vergara 2014 (1.3)	LCF WOMAC		OR 1.47 (95% CI 1.30-1.67) p<0.0001
	SF-12 (PCS)		p=ns
Jones 2017	Baseline function (FIM)		Coef 0.89 (95% CI 0.83-0.95) p<0.001

Appendix table D.5b. Raw extracted data on the functionality at discharge as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Beloosesky 2010	Handgrip strength		beta 0.497 p=0.001
	FIM score		beta 0.261 p=0.001
Ingemarsson 2003 (1.11)	Balance (TUG)		Regression -0.053 SE 0.023 OR 0.95 (95% CI 0.91-0.99) p=0.019
Ingemarsson 2003 (1.12)			Regression -0.022 SE 0.011 OR 0.98 (95% CI 0.96-1.000) p=0.054
Ingemarsson 2003 (1.21)			Regression -0.054 SE 0.020 OR 0.95 (95% CI 0.91-0.99) p=0.009
Ingemarsson 2003 (1.22)			Regression -0.023 SE 0.013 OR 0.97 (95% CI 0.95-1.003) p=0.087

Appendix table D.6. Raw extracted data on the psychological status as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Givens 2008 (1.1)		Depressive symptoms (Geriatric Depression Scale)	OR 0.34 p=0.08
Givens 2008 (1.2)			OR 0.30 p=0.07
Savino (2013)		Depressive symptoms (Geriatric Depression Scale)	OR 0.60 (95% CI 0.35-1.03) p=ns
Vergara 2014 (1.1)		SF-12 mental component summary score (MCS)	OR 0.75 (95% CI 0.60-0.94) p=0.012
Vergara 2014 (1.2)		SF-12 mental component summary score (MCS)	OR0.66 (95% CI 0.52-0.84) p=0.001
Vergara 2014 (1.3)		SF-12 mental component summary score (MCS)	OR 0.70 (95% CI 0.54-0.92) p=0.011
Fortinsky 2002		Rehabilitation therapy self-efficacy	OR 1.18 (95% CI 0.99-1.42) p=0.07
Ingemarsson 2003 (1.11)		Motivation	na (p=ns)
Ingemarsson 2003 (1.12)			na (p=ns)
Ingemarsson 2003 (1.21)			na (p=ns)
Ingemarsson 2003 (1.22)			na (p=ns)
Marottoli 1992		Emotional support	Estimate -0.396 SE 0.204 p=0.057
		Depression (CES-D)	Estimate 0.035 SE 0.015 p=0.022

Appendix table D.7. Raw extracted data on cognition as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Pajulammi 2015	Memory disorder		OR 1.89 (95% CI 1.19–3.00) p=s
Pioli 2016 (1.1)	SPMSQ	Continuous	p=0.159
		No	Ref
		Mild-moderate	HR 1.12 (95% CI 0.53-na) p=0.762
		Severe	NA
Pioli 2016 (1.2)		Continuous	p=0.100
		No	Ref
		Mild-moderate	HR 0.67 (95% CI 0.29–1.58) p=0.635
Pioli 2016 (1.3)		Severe	HR 0.27 (95% CI 0.08–0.90) p=0.033
		Continuous	p=0.932
		Mild-moderate	Ref
		Severe	HR 0.43 (95% CI 0.03-5.79) p=0.754
			HR 0.38 (95% CI 0.02-6.35) p=0.963
Savino 2013	Cognitive impairment	SPMSQ <8	OR 0.99 (95% CI 0.56-1.73) p=ns
Penrod 2008 (1.11)	Dementia		OR 0.43 (95% CI 0.30-0.60) p<0.0001
Penrod 2008 (1.12)			OR 0.65 (95% CI 0.47-0.93) p=0.02
Penrod 2008 (1.21)			OR 0.25 (95% CI 0.17-0.36) p<0.0001
Penrod 2008 (1.22)			OR 0.26 (95% CI 0.18-0.39) p<0.0001
Pareja 2017	GDS		B -3.543 (95% CI -6.384,-0.702) p=0.015
Givens 2008 (1.1)	Cognitive impairment	BDRS ≥4 and MMSE <27	OR 1.11 p=0.84
	Cognitive and mood disorders (combined)		OR 1.01 p=0.96
Givens 2008 (1.2)	Cognitive impairment		OR 1.20 p=0.72
	Cognitive and mood disorders (combined)		OR 0.93 p=0.79
Marottoli 1992	SPMSQ	0-10	Estimate -0.097 SE 0.05 p=0.056
Jones 2017	MMSE	≥18 (ref)	Coef -4.78 (95% CI -8.47;-1.09) p=0.011
Hannan 2001	Dementia		Parameter estimate -0.739, p=0.09
Tarazona 2015	GDS	Normal	Ref
		Mild	OR 0.751 (95% CI 0.433-1.301) p=0.307
		Moderate	OR 0.487 (95% CI 0.251-0.945) p=0.033
		severe	OR 0.439 (95% CI 0.197-0.919) p=0.044

Appendix table D.8. Raw extracted data on comorbidities as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Koval 1998 (2.11)	Number of comorbidities		p<0.05
	ASA	Ref: <2	p=ns
Koval 1998 (2.12)	Number of comorbidities		p=ns
	ASA	Ref: <2	p=ns
Koval 1998 (2.21)	Number of comorbidities		p=ns
	ASA	Ref: <2	p=ns
Koval 1998 (2.22)	Number of comorbidities		p=ns
	ASA	Ref: <2	p=ns
Osnes 2004 (1.1)	Health status	Excellent	Ref
		Good	OR 1.76 (95% CI 0.99-3.14) p=s
		Fair	OR 2.15 (95% CI 1.14-4.04) p=s
		Poor	OR 2.84 (95% CI 1.03-7.85) p=s
Gumieiro 2013 (1.2)	ASA		OR 1.684 (95% CI 0.830-3.416) p=0.15
Moerman 2018	ASA		B 2.69 beta 0.06 T 1.99 p=0.048
Hannan 2001	Modified APACHE		Estimate -0.090 p=0.23
	Modified RAND		Estimate -0.080 p=0.18
Pioli 2016 (1.1)	APS of APACHE II		HR 0.88 (95% CI 0.73–1.05) p=0.162
	CCI		HR 0.69 (95% CI 0.54–0.87) p=0.002
Pioli 2016 (1.2)	APS of APACHE II		HR 0.97 (95% CI 0.84–1.13) p=0.723
	CCI		HR 1.01 (95% CI 0.82–1.25) p=0.914
Pioli 2016 (1.3)	APS of APACHE II		HR 1.06 (95% CI 0.82–1.38) p=0.647
	CCI		HR 0.86 (95% CI 0.66–1.12) p=0.270
Iaboni 2017	Baseline CIRS-G score		Coef -0.056 Exp(Coef) 0.946 SE Coef 0.022 z -2.59 pr>z 0.010
Tarazona 2015	CCI		OR 1.012 (95% CI 0.915-1.118) p=0.817
Savino 2013	CCI	0	Ref
		1	OR 0.92 (95% CI 0.42-2.01) p=ns
		2	OR 0.57 (95% CI 0.26-1.25) p=ns
		>2	OR 0.85 (95% CI 90.40-1.78) p=ns
Jones 2017	Chronic conditions		Coef -3.36 (95% CI -5.30;-1.41) p<0.001
Aigner 2017 (1.11)	Admission 3m prior		B -9.918 â -0.124 (95% CI −19.001; −0.835) p=0.032
Aigner 2017 (1.12)			B -10.025 â -0.117 (95%CI −20.958; 0.909) p=0.072
Aigner 2017 (1.21)			B -2.914 â -0.121 (95% CI −1.992; −0.047) p=0.047
Aigner 2017 (2.22)			B -4.680 â -0.179 (95% CI −8.042; −1.319) p=0.007
Specific comorbidities			
Beloosesky 2010	DASH		Beta -0.255 p=0.005
Gatot 2016	Arthritis		B 1.855 OR 6.389 (95% CI 0.658-62.014) p=0.110
	hypercholesterolemia		B 0.990 OR 2.692 (95% CI 1.323-5.479) p=0.006

Appendix table D.8. Raw extracted data on comorbidities as a prognostic factor of functional outcome. (continued)

Study	Factor	Category	Coefficients, p-values
Koval 1998 (2.11)	Previous hip fracture		p=ns
Koval 1998 (2.12)			p=ns
Koval 1998 (2.21)			p=ns
Koval 1998 (2.22)			p=ns
Osnes 2004 (1.1)	Previous/later fracture hip		OR 2.45 (95% CI 1.12-5.36) p=s
Kim 2012	Previous fracture		HR 0.58 (95% CI 0.26-0.97) p=0.018
Kim 2012	Cancer		HR 3.29 (95% CI 1.64-6.34) p<0.001
Penrod 2008 (1.11)	Cancer		OR 0.91 (95% CI 0.62-1.35) p=0.66
Penrod 2008 (1.12)			OR 0.92 (95% CI 0.67-1.26) p=0.61
Penrod 2008 (1.21)			OR 1.07 (95% CI 0.65-1.73) p=0.19
Penrod 2008 (1.22)			OR 1.02 (95% CI 0.73-1.42) p=0.91
Penrod 2008 (1.11)	Hypertension		OR 0.99 (95% CI 0.76-1.28) p=0.85
Penrod 2008 (1.12)			OR 1.02 (95% CI 0.83-1.27) p=0.92
Penrod 2008 (1.21)			OR 1.01 (95% CI 0.73, 1.40) p=0.13
Penrod 2008 (1.22)			OR 0.89 (95% CI 0.71-1.10) p=0.30
Penrod 2008 (1.11)	COPD/Asthma		OR 0.72 (95% CI 0.50-1.04) p=0.08
Penrod 2008 (1.12)			OR 0.95 (95% CI 0.69-1.31) p=0.75
Penrod 2008 (1.21)			OR 1.45 (95% CI 0.85-2.48) p=0.17
Penrod 2008 (1.22)			OR 0.81 (95% CI 0.58-1.14) p=0.18
Penrod 2008 (1.11)	DM		OR 0.84 (95% CI 0.59-1.18) p=0.32
Penrod 2008 (1.12)			OR 0.98 (95% CI 0.72-1.33) p=0.88
Penrod 2008 (1.21)			OR 0.89 (95% CI 0.58-1.37) p=0.60
Penrod 2008 (1.22)			OR 0.88 (95% CI 0.63-1.22) p=0.45
Penrod 2008 (1.11)	Parkinson		OR 1.00 (95% CI 0.58-1.73) p=0.99
Penrod 2008 (1.12)			OR 0.37 (95% CI 0.22-0.66) p=0.001
Penrod 2008 (1.21)			OR 0.79 (95% CI 0.43-1.47) p=0.46
Penrod 2008 (1.22)			OR 0.65 (95% CI 0.39-1.09) p=0.10
Penrod 2008 (1.11)	Arrythmia		OR 0.86 (95% CI 0.61-1.19) p=0.33
Penrod 2008 (1.12)			OR 0.71 (95% CI 0.52-0.98) p=0.04
Penrod 2008 (1.21)			OR 0.83 (95% CI 0.50-1.28) p=0.39
Penrod 2008 (1.22)			OR 0.85 (95% CI 0.60-1.18) p=0.33
Penrod 2008 (1.11)	Angina pec		OR 0.92 (95% CI 0.59-1.41) p=0.73
Penrod 2008 (1.12)			OR 0.73 (95% CI 0.49-1.06) p=0.10
Penrod 2008 (1.21)			OR 1.09 (95% CI 0.61-2.00) p=0.30
Penrod 2008 (1.22)			OR 0.92 (95% CI 0.64-1.35) p=0.74
Penrod 2008 (1.11)	Heart failure		OR 0.95 (95% CI 0.63-1.42) p=0.79
Penrod 2008 (1.12)			OR 1.06 (95% CI 0.73-1.55) p=0.76

Appendix table D.8. Raw extracted data on comorbidities as a prognostic factor of functional outcome. (continued)

Study	Factor	Category	Coefficients, p-values
Penrod 2008 (1.21)			OR 1.04 (95% CI 0.64-1.71) p=0.17
Penrod 2008 (1.22)			OR 0.87 (95% CI 0.59-1.29) p=0.50
Penrod 2008 (1.11)	CVA/Stroke		OR 0.73 (95% CI 0.49-1.07) p=0.10
Penrod 2008 (1.12)			OR 0.78 (95% CI 0.54-1.13) p=0.54
Penrod 2008 (1.21)			OR 1.09 (95% CI 0.67-1.80) p=0.72
Penrod 2008 (1.22)			OR 0.48 (95% CI 0.33-0.72) p<0.0001
Penrod 2008 (1.11)	Myocardial ischemia		OR 1.11 (95% CI 0.72-1.72) p=0.64
Penrod 2008 (1.12)			OR 1.22 (95% CI 0.86-1.78) p=0.25
Penrod 2008 (1.21)			OR 1.45 (95% CI 0.82-2.60) p=0.20
Penrod 2008 (1.22)			OR 0.97 (95% CI 0.67-1.41) p=0.88
Vergara 2014 (1.1)	Cerebrovascular disease		OR 3.04 (95% CI 1.11-8.34) p=0.031
Vergara 2014 (1.2)			p=ns
Vergara 2014 (1.3)			p=ns

Appendix table D.9. Raw extracted data on the nutritional status as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Gumieiro 2013 (1.1)	NRS 2002		OR 1.429 (95% CI 0.686-2.275) p=0.47
Gumieiro 2013 (1.3)	MNA		OR 0.773 (95% CI 0.663-0.901) p=0.001
Pioli 2016 (1.1)	Albumin	<3.2g/dl (ref)	HR 0.47 (95% CI 0.22–0.99) p=0.049
Pioli 2016 (1.2)			HR 0.82 (95% CI 0.36–1.86) p=0.635
Pioli 2016 (1.3)			HR 0.81 (95% CI 0.29–2.36) p=0.703
Pareja 2017	nutritional supplements at discharge		B 9.611 (95% CI 1.497,-17.724) p=0.21
Pajulammi 2015	BMI	23-28	Ref
		<23	OR 1.35 (95% CI 0.87-2.10) p=ns
		>28	OR 1.08 (95% CI 0.71-1.63) p=ns
Helminen 2017 (1.1)	MNA-SF	Normal	Ref
		At risk	HR 1.81 (95% CI 1.17-2.80) p<0.10
		Malnourished	HR 2.37 (95% CI 0.88-6.38) p<0.10
Helminen 2017 (1.2)		Normal	Ref
		At risk	HR 1.88 (95% CI 1.18-2.99) p<0.10
		Malnourished	HR 3.28 (95% CI 0.97-11.0) p<0.10
Helminen 2017 (1.3)	Albumin	34-45g/l	Ref
		28-33g/l	HR 1.16 (95% CI 0.72-3.86) p>=0.10
		<28g/l	HR 1.52 (95% CI 0.60-3.86) p>=0.10

Appendix table D.10. Raw extracted data on the vitamin D status as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Gumieiro 2015	Calcifediol	< 20 ng/mL	HR 1.463 (0.524–4.088) p=0.469
Savino (2013)	Calcifediol	Lowest tertile	Ref
		Intermediate	OR 1.89 (95% CI 1.01-3.54) p=s
		Highest	OR 2.29 (95% CI 1.22-4.28) p=s
Pioli 2016 (1.1)	Calcifediol	<6ng/ml ref	Ref
		6-11ng/ml	HR 1.81 (95% CI 0.76–4.28) p=0.180
		>11ng/ml	HR 2.9 (95% CI 1.23–6.85) p=0.015
Pioli 2016 (1.2)		<6ng/ml	Ref
		6-11ng/ml	HR 2.81 (95% CI 1.21–6.51) p=0.016
		>11ng/ml	HR 3.66 (95% CI 1.47–9.11) p=0.005
Pioli 2016 (1.3)		<6ng/ml	Ref
		6-11ng/ml	HR 0.81 (95% CI 0.22–3.05) p=0.523
		>11ng/ml	HR 1.03 (95% CI 0.27–3.90) p=0.496
Carpintero 2006	Calcifediol	25–113 nmol/l	OR 2.7 (95% CI -0.7-9.9) p=0.13
Carpintero 2006	Calcitriol	48–110 pmol/l	OR 6.97 (95% CI -1.7–27.4) p=0.005

Appendix table D.11. Raw extracted data on the fracture type as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Jones 2017	Fracture type	FNF	Ref
		Intertrochanteric	Coef -2.08 (95% CI -3.82;-0.34) p=0.019
		Subtrochanteric/combination	Coef -7.67 (95% CI -11.84;-3.49) p<0.001
Kim 2012	Fracture type	FNF (ref)	HR 1.11 (95% CI 0.63-1.55) p=0.742
Pajulammi 2015	Fracture type	FNF	Ref
		Intertrochanteric	1.46 (0.996-2.15) p=ns
		Subtrochanteric	1.00 (0.45–2.22) p=ns
Cornwall 2004 (1.3)			p=ns
Cornwall 2004 (1.4)			p=ns
Koval 1998 (2.11)	Fracture type	FNF (ref)	na (p=ns)
Koval 1998 (2.12)			na (p=ns)
Koval 1998 (2.21)			na (p=ns)
Koval 1998 (2.22)			na (p=ns)

Appendix table D.12. Raw extracted data on the delay in surgery as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Kim 2012		Delay in surgery >2days	HR 1.49 (95% CI 0.94-2.32) p=0.039
Pioli 2016 (1.1)		Surgery <48h (ref)	HR 0.95 (95% CI 0.49–1.84) p=0.870
Pioli 2016 (1.2)			HR 1.07 (95% CI 0.52–2.21) p=0.860
Pioli 2016 (1.3)			HR 1.53 (95% CI 0.48–4.84) p=0.468
Savino 2013	Time to surgery	Lowest (tertile)	Ref
			Intermediate OR 1.72 (95% CI 0.98-3.02) p=ns
			Highest OR 1.35 (95% CI 0.61-2.96) p=ns

Appendix table D.13. Raw extracted data on complications as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Moerman 2018	Postoperative complications		B 3.53 beta 0.10 T 2.83 p=0.005
Pioli 2016 (1.1)	Delirium		HR 0.48 (95% CI 0.21-1.10) p=0.084
Pioli 2016 (1.2)			HR 0.99 (95% CI 0.43-2.29) p=0.978
Pioli 2016 (1.3)			HR 0.36 (95% CI 0.11-1.22) p=0.100
Tarazona 2015	Delirium		HR 0.692 (95% CI 0.433-1.107) p=0.125
Corcoles 2015	Without complications after discharge		B -1.205 Exp(B) 0.3 (95% CI 0.133-0.674) p=0.004
Givens 2008 (1.1)	Delirium		OR 2.35 p=0.07
Givens 2008 (1.2)			OR 2.10 p=0.12

Appendix table D.14. Raw extracted data on the remaining factors as a prognostic factor of functional outcome.

Study	Factor	Category	Coefficients, p-values
Osnes 2004 (1.1)	Site of accident	Indoor	Ref
		Outdoor	OR 0.44 (95% CI 0.27-0.72) p=s
		In traffic	OR 0.49 (95% CI 0.15-1.66) p=ns
		Unrecorded	OR 0.61 (95% CI 0.32-1.18) p=ns
	Trauma mechanism	HET (ref)	OR 1.24 (95% CI 0.59-2.60) p=ns
Koval 1998 (1.11)	Anesthesia type	General	na, p=ns
Koval 1998 (1.12)			na, p=ns
Koval 1998 (1.21)			na, p=ns
Koval 1998 (1.22)			na, p=ns
Moerman 2018	Length of hospital stay		B 0.26 beta 0.12 T 3.70 p=0.000
Savino 2013	Early rehabilitation		OR 2.38 (95% CI 0.92-6.16) p=ns
Gumieiro 2013	225 kDa (homodimer pro-MMP 9)		OR 1.03 (95% CI 0.94-1.12) p=0.55
Gumieiro 2013	72 kDa (pro-MMP 2)		OR 1.21 (95% CI 1.03-1.43) p=0.02
Gumieiro 2013	92 kDa (pro-MMP 9)		OR 0.97 (95% CI 0.90-1.04) p=0.34
Gumieiro 2013	130 kDa (pro-MMP 9 +NGAL)		OR 0.98 (95% CI 0.92-1.05) p=0.52
Ingemarsson 2003 (1.11)	Peak expiratory flow		na, p=ns
Ingemarsson 2003 (1.12)			na, p=ns
Ingemarsson 2003 (1.21)			na, p=ns
Ingemarsson 2003 (1.22)			na, p=ns
Iaboni 2017	Potentially inappropriate medication (PIM) user		Coef -0.371 Exp coef 0.690 SE coef 0.147 z -2.52 p>z 0.012
Iaboni 2017	Postoperative pain		Coef -0.092 Exp coef 0.913 SE coef 0.028 z -3.32 pr>z 0.001
Pajulammi 2015	Urinary catheter removed during hospital stay		OR 0.45 (95% CI 0.29-0.70) p=s

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Chapter 6

Short-term recovery of independence in a multi-state model

Prognostic factors for short-term recovery of independence in a multi-state model for patients with a hip fracture. van der Sijp M.P.L., van Eijk M., Niggebrugge A.H.P., Putter H., Blauw G.J., Achterberg W.P. *J Am Med Dir Assoc. 2020 Sep 19;S1525-8610(20)30696-4.*

Abstract

Objectives: This study investigates the transitions of community-dwelling patients with a proximal femoral fracture towards recovery of independence using multistate modeling. The prognostic value of factors affecting the short-term rate of recovery of independence in activities of daily living was assessed for the resilient portion of the population.
Design: An inception cohort was recruited between 2016 and 2019.
Setting and Participants: Only community-dwelling older patients admitted with a proximal femoral fracture were included.
Measures: Follow-up was performed at 6 weeks and 3 months, when the patients' living situation and level of independence were recorded. Multistate modeling was used to study the transition rates of the population through prespecified states of the recovery process. Using this model, prognostic factors for the recovery of independence were identified for resilient patients (defined as those patients who managed to return home at any point in the follow-up after discharge).
Results: A total of 558 patients were included, and 218 (40.9%) recovered to prefracture levels of independence. Of the resilient patients, 20.7% were discharged home directly, and 79.3% via a rehabilitation home. In this patient group, a more favorable American Society of Anesthesiologists classification, better prefracture mobility, and the absence of a prefracture fear of falling were statistically significantly associated with a successful recovery. A low level of prefracture independence was inversely associated, meaning that patients with a low level of prefracture independence had a higher chance of successful recovery.
Conclusions and Implications: This study identified 4 factors with an independent prognostic value for the recovery of independence in resilient patients after a proximal femoral fracture. These factors could be used to construct clinical profiles that contribute to the assessment of the patient's post-acute care needs and recovery capacity. In addition, multistate modeling has been shown to be an effective and versatile tool in the study of recovery prognostics.

Introduction

Despite the frequent presence of frailty characteristics, the majority of patients admitted with a proximal femoral fracture were independently living patients with a high level of independence in activities of daily living (ADL) before the occurrence of the fracture.1 Of these patients, an estimated 12-19% dies within one year after surgery and another 10-20% becomes permanently institutionalized.2, 3 Those who do regain sufficient independence and avoid institutionalization display considerable physical resilience.[4] Regardless, up to 80% of patients who are able to return to their independent living situation do not fully recover to prefracture level of independence in ADL.[3] This has substantial personal and social implications for the patient as an individual and a significant economic impact on the healthcare system.

This combination of recovery goals (survival, returning home and recovering independence) is often studied using separate analyses for each of the alternative outcomes (events). This may, however, not be completely correct, since this approach fails to reveal possible relationships between the different events. Events may be competing with one another, meaning they could influence each other if and when another event occurs.[5] In the case of the recovery of independence in patients with a hip fracture, the alternative events of mortality or admission to a nursing home may compete with each other. Previous studies of functional recovery have often either excluded patients who died during follow-up, as their functional status couldn't be assessed after that event, or have opted to allocate these patients to an unfavorable outcome category.[6-8] In those studies, no adjustment was made for competing events.

Multistate modeling is a novel technique that takes patient transitions throughout the recovery process into account. As such, multistate models allow inclusion of all potentially competing events. In addition, the probability and rate of patient transitions through the states of the model can be estimated for each time point in the process. The prognostic value of patient and treatment factors can be assessed in relation to each transition and the rate of a particular transition, allowing the relevance of each factor to be estimated at every step of the recovery process.[9]

A recent review by Sheehan et al. (2018) identified 25 factors for which the prognostic value of short-term functional outcome was tested. Sufficient but still only weak levels of evidence were found for anemia and impaired cognition, and both were negatively associated with regaining function.[10] Previously identified prognostic factors for loss of independence include age, comorbidity scores, cognitive status and pre-fracture functionality.[11-14] Besides these predominantly biological factors, some psychosocial factors have also been associated with functional outcome, including fear of falling and presence of an informal caregiver.[15, 16]

A better understanding of the relevance of these factors for the recovery of independence would improve prognostics, which is valuable for the management of patient expectations and helps to anticipate the need for appropriate care appropriately when a prolonged functional deficit is expected. For the more resilient patients who are discharged home, this information would be relevant to homecare and the burden on informal caregivers such as partners and family.

Using multistate modeling, this study investigates the transitions related to the recovery of independence in community-dwelling patients with a proximal femoral fracture. Focusing on the resilient portion of the population, the prognostic value of factors related to the short-term rate of recovery of independence in activities of daily living are assessed.

Methods

This prospective cohort study was performed and documented in agreement with the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' statement guidelines for reporting observational studies.[17] Data were handled in accordance with 'Good Research Practice' guidelines. Data were registered prospectively in a coded database, concurrently with clinical registrations during admission. Details of the routine data collection and outcomes have been published previously and apply to all patients with a proximal femoral fracture.[18]

The methodology of data collection and of any subsequent observational studies was approved by the institutional Medical Research Ethics Committee and the study hospital's board of directors without the need for individual patient consent.

Patients

An inception cohort was constructed that included all patients admitted with a proximal femoral fracture between December 2016 and December 2019. Inclusion in the final study cohort was limited to older patients (aged 70 years or more) who were community-dwelling, which was defined as not permanently residing in a nursing home before admission. Exclusion criteria included patients with high-energy traumas or pathological fractures.

Treatment and assessments

Baseline characteristics and details of treatment were registered during admission. These included age, sex, general health status using the American Society of Anesthesiologists (ASA) classification (categorized as I-II and III-V)[19], nutritional status using the Mini Nutritional Assessment - Short Form (MNA®-SF, categorized as normal, 14-12 or abnormal 11-0)[20, 21], prefracture residence (categorized as at home, at home with homecare or a residential home), the availability of an informal caregiver at home, fracture type and treatment type. Cognition was rated using the Six-item Cognitive Impairment Test (6CIT) upon admission, with cognitive impairment defined as a score ≥11 or as a previous diagnosis of dementia.[22] The (prefracture) baseline of independence in activities of daily living (using the Katz Index of Independence in Activities of Daily Living, Katz ADL)[23], mobility (using the Parker Mobility Score, PMS)[24], and fear of falling[25] were retrospectively assessed during admission, taking the period directly before the fracture. Anemia was recorded based on routine bloodwork during admission and categorized as a hemoglobin level below 8.1 mmol/L (12 g/dL) for men and below 8.1 mmol/L (13 g/dL) for women.

During the acute hospital phase, postoperative patients were discussed twice weekly in a multidisciplinary meeting that included an orthopedic trauma surgeon, ward doctor, geriatrician, trauma nurse, physiotherapist and transfer nurse. Patients were preferably discharged 3 days after surgery, if pain was manageable and no active complications were present. For prefracture community-dwelling patients, discharge home was generally possible when mobility was adequate for independent living (meaning that the patient could safely make indoor transfers) or if home care was available and sufficient (or redundant). If not, or if rehabilitation goals were too complex to be dealt with through ambulatory therapy, discharge to a geriatric rehabilitation nursing home was planned.[26] In the Netherlands, geriatric rehabilitation is a form of temporary inpatient care at a specialized nursing home, led by an elderly care physician for an intended period of 6 weeks to 3 months. Nursing staff and an occupational therapist are involved in the recovery of independence in ADL, such as transferring and bathing. Patients receive on average 3-6 sessions of physiotherapy per week, though intensity varies depending on the patients' physical endurance and formalized agreements employed by the rehabilitation units.[27] Additional treatment aspects during geriatric rehabilitation concern general medical care, fall prevention, osteoporosis, nutrition and fear or depression.

Patients were invited for routine outpatient check-ups 6 weeks and 3 months after surgery. Patients not attending the outpatient check-ups were called to reschedule or, if not possible, to arrange a check-up by phone. Patients for whom an outpatient checkup was deemed too burdensome, due to severe cognitive or physical impairments also had a phone check-up. The Katz ADL and current living situation were assessed and recorded.

Outcomes and the multistate model

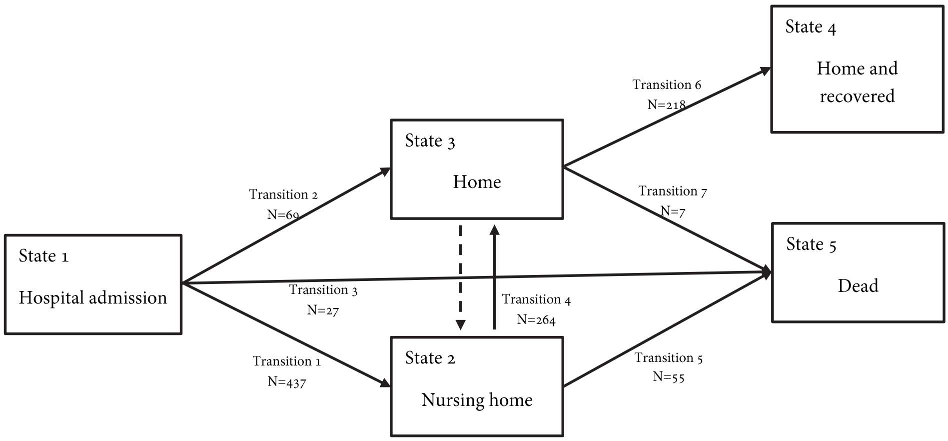
The primary outcome and endpoint of recovery in this study is a combined outcome measure for the recovery of independence in ADL. Recovery was considered successful when patients simultaneously met all three criteria stated below on at least one of the two outpatient check-ups (6 weeks or 3 months after surgery) during follow-up;

- No mortality due to any cause.
- Independent living: the patient returned to an independent form of residency. Residence was grouped binomially as dependent (included residence in a geriatric rehabilitation home or a nursing home) or independent (living in a private residency with or without homecare, or in a residential home).

- Recovery of independence in ADL: assessed using the Katz ADL score, and patients who returned to their prefracture level of independence in ADL (follow-up Katz ≤ prefracture Katz) were considered successful.

Here, the criteria 'mortality' and 'independent living' are considered inherent aspects of the recovery of independence in ADL. In the multistate model, each of these events is an individual state. The model consists of 5 states in total: (1) hospital admission from surgery to discharge, (2) residing in a nursing home, either temporarily for geriatric rehabilitation, or secondarily and permanently after unsuccessful rehabilitation, (3) residing in an independent living situation (including homecare or a residential home), (4) independent living with recovered independence in ADL and (5) deceased (Figure 1). States 4 and 5 were included as absorbing states, meaning patients are censored when reaching these states. The transition from home to a nursing home (3 à 2) was observed for only 3 (0.6%) cases and excluded from the model. Hospital readmission (a return to state 1) was not included in the model.

Figure 1. Multi-state model representing the states from admission to recovery or dead and their interlinking transitions within 3 months.



Each box represents a possible postoperative state. The arrows represent the observed transitions of patients between states within the 3-month follow-up period. The dotted arrow was a state transition that was rarely observed and therefore excluded from further analyses. Patients were only considered 'recovered' (state 4) when they were alive, lived independently, and had a recovered independence in activities of daily living.

Statistical analyses

No missing data were imputed. Univariate analyses were used to compare the baseline characteristics with regard to the primary outcome. An unpaired two-sample t-test was used to compare means, with standard deviations (SD), of continuous data with a normal distribution. Data with a non-normal distribution (Kolmogorov-Smirnov test of $p < 0.05$), are presented as medians with interquartile ranges (IQR) and compared using the Mann–Whitney U test. Categorized characteristics were compared using crosstabs and the Chi-square test if the groups were sufficiently large (expected cell-count <5) or Fishers-exact test if this condition was not met.

Multistate analyses were used to assess the influence of factors on the participants' transition rates to a recovered independence in ADL and to independent living.[5, 28] In order to model effects on the functional recovery of the more resilient patients who returned to their prefracture independent living situation, all 11 patient characteristics were included as factors in the multistate analyses for patients transitioning to the 'home and recovered' state (state 6).

All statistical analyses were performed using IBM SPSS statistics PC software version 25.0 and the package mstate (de Wreede et al. 2010) version 0.2.11, for R version 3.6.1 (R Development Core Team 2006).[29] A p-value smaller than 0.05 was considered statistically significant. A convenience sample size was used by including all patients from the prespecified inclusion period.

Results

Between December 2016 and December 2019, a total of 558 eligible patients were admitted with a proximal femoral fracture. Sufficient follow-up data were obtained for 533 (95.5%) patients, and 97.5% of all characteristics data were available for these patients. The median age of patients was 85 (IQR 77-90) and a majority were female (n=235, 71.5%). Regarding fractures, 282 (52.9%) patients had a femoral neck fracture, 234 (43.9%) patients had a pertrochanteric femoral fracture and 17 patients (3.2%) a subtrochanteric fracture. An osteosynthesis was performed for 297 (55.7%) patients, a prosthesis for 226 (42.4%) patients, and 11 (2%) patients were treated conservatively (Table 1).

The median follow-up for all patients was 87 (IQR 11) days, and the 3-month follow-up was planned a mean 90 (SD ±9.3) days after treatment. Regarding the baseline characteristics of included patients, those who recovered within 3 months of surgery (n=218, 40.9%) were significantly younger and had a more favorable ASA classification, mobility, independence in ADL, cognition, nutritional status, prefracture living situation and fear of falling status (Table 1). Sixty-nine (12.9%) patients were discharged home directly, 438 (82.0%) were discharged to a nursing home (either for rehabilitation or for permanent stay), and 27 (5.1%) patients died during their hospital stay (Figure 1). Of the patients discharged to a nursing home, 264 (60.4%) were discharged home within the study period. Of the patients who returned home after discharge, 218 (65.5%) recovered to their prefracture level of independence in ADL.

The distribution of patients in each state over time is presented in Figure 2. The transition of patients to the 'recovered' state at 45 and 90 days (seen as inversed sigmoid curves in the graph) corresponds to the outpatient check-ups assessing patient independence of ADL at 6 weeks and 3 months after surgery.

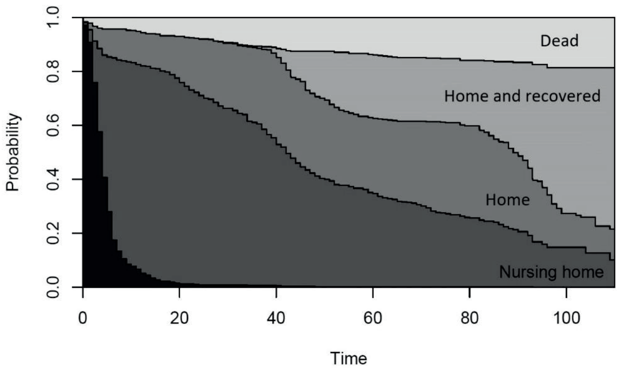
Table 1. Baseline characteristics for patients with a proximal femoral fracture stratified for functional outcome.

Characteristic	**Unrecovered N=315 (59.1%)**	**Recovered N=218 (40.9%)**	**All patients N=533 (100%)**	**P-value**
Patient characteristic				
Age, years (median, IQR)	87 (80-91)	80 (75-87)	85 (12)	*<0.001*
Sex, female	231 (73.3)	150 (68.8)	381 (71.5)	0.26
ASA classification				
I-II	87 (27.6)	105 (48.2)	192 (36.0)	
III-V	228 (72.4)	113 (51.8)	341 (64.0)	*<0.001*
Parker mobility score				
7-9	93 (30.0)	147 (67.7)	240 (45.5)	
4-6	164 (52.9)	57 (26.3)	221 (41.9)	
0-3	53 (17.1)	13 (6.0)	66 (12.5)	*<0.001*
Katz ADL score				
0-1	183 (58.7)	163 (74.8)	346 (65.3)	
2-3	71 (22.8)	37 (17.0)	108 (20.4)	
4-6	58 (18.6)	18 (8.3)	76 (14.3)	*<0.001*
Cognitive impairment	138 (47.6)	53 (25.9)	191 (38.6)	*<0.001*
Malnourished	146 (49.8)	55 (25.9)	201 (39.8)	*<0.001*
Living situation				
Independent	160 (50.8)	163 (74.8)	323 (60.6)	
Homecare or residential home	155 (49.2)	55 (25.2)	210 (39.4)	*<0.001*
Informal caregiver				
Yes	190 (62.3)	124 (57.1)	314 (60.2)	0.24
Fear of falling				
Yes	153 (56.7)	77 (37.9)	230 (48.6)	*<0.001*
Anemia				
Yes	154 (49.0)	89 (41.0)	243 (45.8)	0.068

ASA, American Society of Anesthesiologists; IQR, interquartile range. Higher ASA scores represent more severe comorbidities; higher Katz ADL scores represent lower levels of independency; and higher Parker Mobility Scores represent better levels of mobility. Recovered patients regained their individual prefracture level of independence in ADL. Italics indicate a P value of < .05.

The following factors were identified as significantly associated with a successful recovery of independence in ADL (Table 2): a less severe ASA classification (HR, 0.68; 95% CI, 0.49-0.95; P = 0.025), a better prefracture mobility (HR, 0.61; 95% CI, 0.39-0.95; P = 0.028 and HR, 0.31; 95% CI, 0.13-0.78; P = 0.013), a lower level of prefracture independence in ADL (HR, 2.53; 95% CI, 1.31-4.88; P = 0.006 and HR, 3.42; 95% CI, 1.66-7.03; P = 0.001) and the absence of prefracture fear of falling (HR, 0.65; 95% CI, 0.48-0.90; P = 0.009). Other factors (age, sex, cognition, malnutrition, presence of an informal caregiver, and anemia) did not show a significant association (P > 0.05).

Figure 2. Distribution of patients by state during short-term follow-up of patients with a proximal femoral fracture.



Each level, moving from the lower-left to the upper-right corner, corresponds to a state of the multi-state model: hospital admission, nursing home, home (meaning residing in an independent living situation, also including with homecare or in a residential home), home and functionally recovered, or dead. Time is presented in days from treatment.

Discussion

To our knowledge this is the first study to use multistate modeling to assess factors that may be independently associated with recovery after proximal femoral fracture. In addition, the model provides an overview of the transitions of patients through a set of recovery states. Of the community-dwelling older patients admitted with a proximal femoral fracture, 60.4% returned to independent living and 40.9% recovered to their prefracture level of independence in ADL.

The multistate model analyses, which focused on resilient patients who had reached an independent living situation within three months after treatment, identified four factors as being independently associated with the rate of recovery. These were prefracture mobility, comorbidity, prefracture independence in ADL, and fear of falling. Prefracture functional status and comorbidities have previously been identified as relevant, both in terms of determining a patients' resilience[4] and predicting functional outcomes.[30-32] A poorer rate of recovery in patients who experience fear of falling, especially for those with a high level of premorbid functionality, has also been observed previously.[16] A better prefracture functional status was associated with a more favorable outcome for each of the significant factors identified in this study, except for independence in ADL. We hypothesize that patients with a low level of prefracture independence in ADL lose a relatively lower degree of independence and therefore have less independence to recover, so it is less of an effort for them to return to their prefracture level. This corresponds with previous findings which indicate that most patients recover at similar rates, regardless of their prefracture functional level.[4]

Table 2. Factors independently associated with the rate of short-term recovery for independence in activities of daily living.

Characteristic	**Adjusted* HR (95% CI)**	**P-value**
Age, years	0.98 (0.96-1.00)	0.063
Sex, female	0.85 (0.61-1.19)	0.34
ASA classification		
I-II	1.0 (ref)	
III-IV	0.68 (0.49-0.95)	*0.025*
Parker Mobility Score		
7-9	1.0 (ref)	
4-6	0.61 (0.39-0.95)	*0.028*
0-3	0.31 (0.13-0.78)	*0.013*
Katz ADL score		
0-1	1.0 (ref)	
2-3	2.53 (1.31-4.88)	*0.006*
4-6	3.42 (1.66-7.03)	*0.001*
Cognitive impairment (yes)	1.26 (0.88-1.81)	0.21
Malnourished	1.44 (0.97-2.15)	0.069
Living situation		
Independent	1.0 (ref)	
Homecare or residential home	0.81 (0.47-1.42)	0.47
Informal caregiver (yes)	0.89 (0.66-1.22)	0.47
Fear of falling (yes)	0.65 (0.48-0.90)	*0.009*
Anemia (yes)	1.33 (0.98-1.82)	0.072

ASA, American Society of Anesthesiologists; ref reference category.
N=290; number of events = 188. A total of 43 observations were deleted due to absence. Italics indicate a P-value of <0.05. Higher ASA scores represent more severe comorbidities; higher Katz ADL scores represent lower levels of independency; and higher Parker mobility scores represent better levels of mobility. *Adjusted for all other factors in Table 2.

Consequently, those patients who have less function to regain, will reach their recovery endpoint sooner. Clinicians should be mindful of the expecting recovery rate and assess patients holistically to find underlying causes when a patient diverges from expectations.

Contrary to the findings of a recent systematic review on short-term prognostic factors of functional recovery, cognition and anemia showed no significant association.[10] This might indicate that these factors are relevant for the recovery of patients with proximal femoral fractures in general, but not for the recovery of independence in ADL in resilient patients who have recovered to a state of independent living. Cognitive status is an important factor with regards to discharge location, as patients with a cognitive impairment have a higher likelihood of being admitted to a nursing home. Anemia is most likely associated with elevated mortality rates rather than the recovery capacity of patients. In our multistate model, admission to a permanent nursing home and mortality were competing outcomes with our primary outcome. The analyses, however, focused only on resilient patients who succeeded in returning home, so risk for these competing outcomes is probably smaller in this subgroup compared to the population as a whole. This may explain why the factors cognition and anemia showed no significant associations.

Other variations in the methodology of this study compared to previous studies could in theory also contribute to the inconsistencies in findings. These include differences in overall patient selection, aspects such as the intensity of physiotherapy provided during recovery, the length of follow-up or the definition of functional recovery.

The current findings of this study emphasize the relevance of a holistic approach and systematic assessment of characteristics that have been found relevant by this study. A clinical profile could be constructed using the factors comorbidity, prefracture mobility, prefracture independence in activities of daily living and fear of falling, which help to assess the patients' post-acute care needs, including the needs for support in activities of daily living for patients who manage to return home within 3 months of treatment.

Multistate modeling seems an appropriate and flexible method which provides important insights, that might have otherwise been ignored when using an ordinary regression model.[28] The model allows for analyses of each individual transition, and multiple outcomes. This study focused on a late transition of the patients who had reached and independent form of living (defined as the resilient patients) to a recovered state of independency, in order to study their functional prognosis and the factors relevant for recovery. In addition, multistate 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.[9] Future studies could use the model to predict outcomes at multiple time points, for instance at the moment of hospital discharge and geriatric rehabilitation discharge or during check-ups at specific intervals. This type of application might allow prediction of whether patients will manage independent living or walking without aides in the foreseeable future, and may lead to adjustments of rehabilitation and care aspects accordingly.

Limitations

This study describes a complete inception cohort of older patients with a proximal femoral fracture, and their transitions between states within a short-term recovery period after treatment. An adequate follow-up was achieved for most patients, and the primary combined outcome of this study ensured no loss to follow-up due to mortality.

This study included only older community-dwelling patients, so findings may be limited to this subpopulation. However, older community-dwelling patients form the majority of patients with a proximal femoral fracture. In addition, the recovery of independence in ADL has the most significant social and economic impact in this specific patient group, as they risk additional reliance on (professional) caregivers or loss of independent living and institutionalization.

Follow-up was limited to three months, which roughly corresponds to the duration of geriatric rehabilitation provision in the Netherlands. A longer follow-up could have been considered, but this study focused on resilient patients who generally regain independent living within this time frame. A further possible limitation was that a more complex multistate model could have distinguished between a temporary stay in a geriatric rehabilitation home or discharge to permanent residence in a nursing home. Although this more elaborate model might have provided a more coherent overview, the added value for prognostic purposes could be questioned.

Conclusions and implications

This study identified 4 factors (comorbidity, prefracture mobility, prefracture independence in ADL, and fear of falling) with an independent prognostic value for the recovery of independence among resilient patients after a proximal femoral fracture. A multistate model has been demonstrated to be an effective and versatile tool in the study of recovery prognostics.

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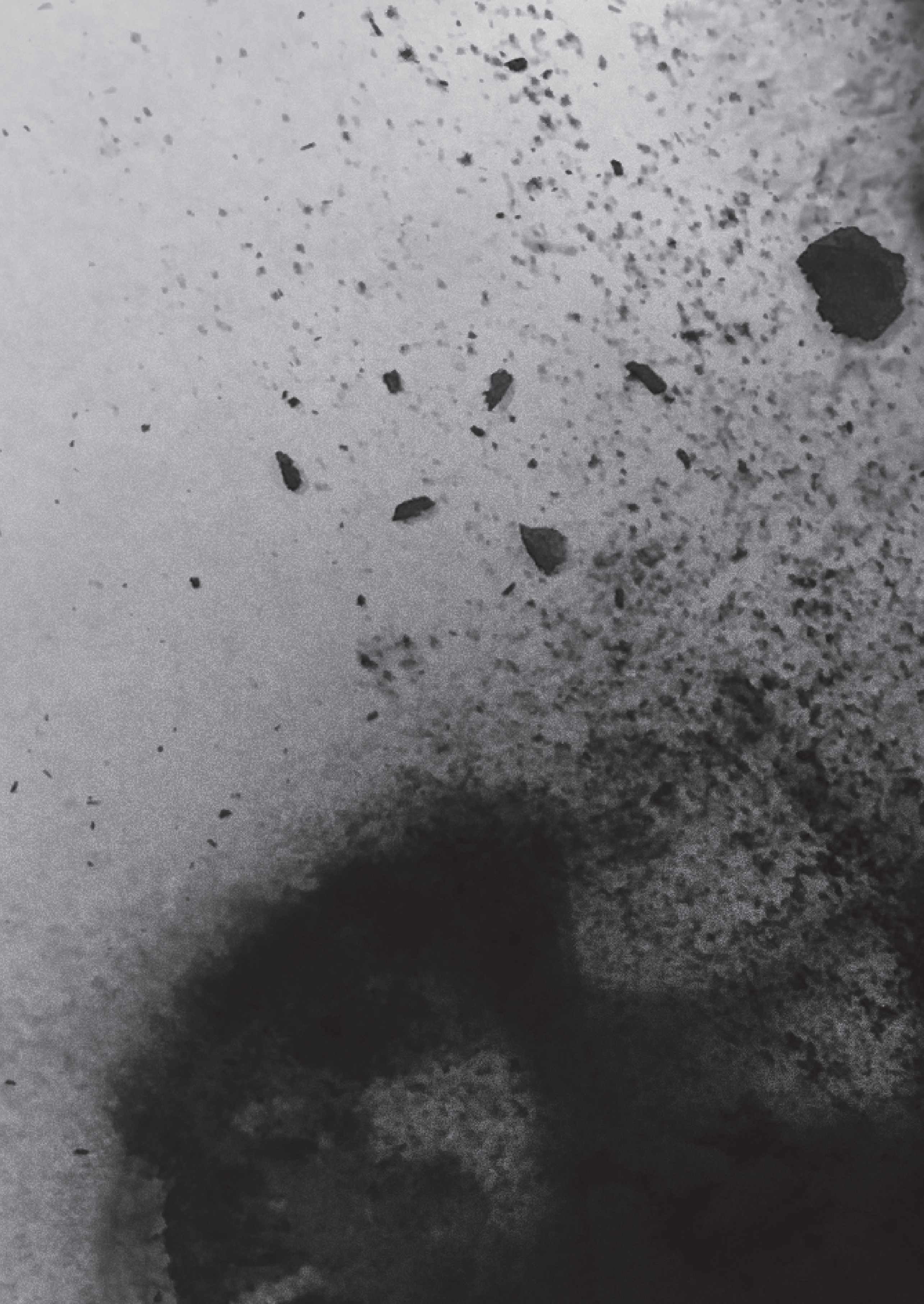

Chapter 7

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.
    - o 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]
    - o The Functional Ambulation Categories (FAC) score is a 6-point scale that facilitates assessment of independence in ambulation through observation of the patient.[42]
    - o 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.

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Chapter 8

The prognostic value of serum metabolites

van der Sijp M.P.L, Suchiman H.E.D., van Eijk M., Vojinovic D., Niggebrugge A.H.P., Blauw G.J., Achterberg W.P., Slagboom P.E. The prognostic value of metabolic profiling in older patients with a proximal femoral fracture. *Geriatr Orthop Surg Rehabil. 2020 Oct 29;11:1-7*.

Abstract

Introduction: High mortality rates of approximately 20% within one year after treatment are observed for patients with proximal femoral fractures. This preliminary study explores the prognostic value of a previously constructed mortality risk score based on a set of 14 metabolites for the survival and functional recovery in patients with proximal femoral fractures.

Materials and methods: A prospective observational cohort study was conducted including patients admitted with a proximal femoral fracture. The primary outcome was patient survival, and the recovery of independence in activities of daily living was included as a secondary outcome. The mortality risk score was constructed for each patient and its prognostic value was tested for the whole population.

Results: Data was available form 136 patients. The mean age of all patients was 82.1 years, with a median follow-up of 6 months. Within this period, 19.0% of all patients died and 51.1% recovered to their prefracture level of independence. The mortality score was significantly associated with mortality (HR, 2.74; 95% CI, 1.61-4.66; $P < 0.001$), but showed only a fair prediction accuracy (AUC = 0.68) and a borderline significant comparison of the mortality score tertile groups in survival analyses ($P = 0.049$). No decisive associations were found in any of the analyses for the functional recovery of patients.

Discussion: These findings support the previously determined prognostic value of the mortality risk score. However, the independent prognostic value when adjusted for potential confounding factors is yet to be assessed. Also, a risk score constructed for this specific patient population might achieve higher accuracies for the prediction of survival and functional recovery.

Conclusions: A modest prediction accuracy was observed for the mortality risk score in this population. More elaborate studies are needed to validate these findings and develop a tailored model for clinical purposes in this patient population.

Introduction

Metabolic profiling in epidemiological or clinical cohorts is the simultaneous measurement of numerous metabolites: molecules involved in metabolic processes. Many metabolites have been identified as biomarkers for aspects of health and disease such as mortality, nutritional state and cognitive ability.[1, 2] As such, metabolic profiling may potentially provide an alternative to clinical data for long-term prognostics.[3-6] A mortality risk score was constructed on the basis of 14 circulating metabolites that were independently associated with mortality in a range of EU population-based cohorts, predicting all-cause 5-10 years mortality.[3] These 14 metabolites are known to be involved in processes including inflammation, glycolysis, fatty acid and lipoprotein metabolism and fluid balance.[3]

High mortality rates of approximately 20% within one year after treatment are observed for patients with proximal femoral fractures.[7-9] Some of the metabolites included in the mortality risk score have also been studied in patients with a proximal femoral fracture.[10] Low levels of the plasma protein albumin, considered an important marker of the nutritional status, is associated with adverse outcomes.[1, 11-13] Other markers that have been associated with mortality by multiple studies in patients with proximal femoral fractures include low preoperative hemoglobin levels[11, 14, 15], low total leucocyte count[11, 16, 17], high creatinine[11, 14], high parathyroid hormone[1, 11, 18], high troponins[19] and high potassium.[14]

Evidence on the value of metabolic profiling for the prognostics of functional recovery in fracture patients is more limited. Only anemia on admission was deemed a relevant prognostic factor with a weak level of evidence in a recent systematic review regarding functional recovery.[20] Studies on albumin and vitamin D did not present convincing evidence.[20]

Assessments of metabolites associated with the outcomes after a proximal femoral fracture may potentially improve the prognostic accuracy, and further substantiate the metabolomic relevance for patient outcomes.[1] A pilot study was conducted using a newly constructed cohort of older patients with proximal femoral fractures. This preliminary study explores the prognostic value of a previously constructed mortality risk score based on a set of 14 polar metabolites, lipoproteins, fatty acids and inflammatory proteins for the survival and functional recovery in patients with proximal femoral fractures.

Methods

Patients

A single-center prospective observational cohort study included patients with a proximal femoral fracture admitted between December 2019 and May 2020. All patients with pathological fractures, bilateral fractures and less than 18 years of age were excluded.

Treatment and assessments

Patients were treated with routine care and data were registered in a coded database by the treating physicians. No individual informed consents were obtained due to the observational nature of the study and the use of routinely collected anonymous data and samples only.

The registered baseline characteristics included age, sex, general health status using the American Society of Anesthesiologists classification[21], nutritional status using the Mini Nutritional Assessment - Short Form[22, 23], prefracture residency (categorized as at home, at home with homecare or a residential home, or a nursing home) and cognitive impairment (defined as any previously diagnosed form of dementia or a Six-item Cognitive Impairment Test ≥11 upon admission). The (prefracture) baseline of independence in activities of daily living (Katz Index of Independence in Activities of Daily Living, Katz ADL)[24] and mobility (the Parker Mobility Score)[25] were assessed retrospectively during admission, considering the period directly before the fracture. The fractures were classified as either femoral neck fractures or (sub)trochanteric fractures. Treatment type (osteosynthesis, prosthesis or conservatively) was registered before discharge. Prefracture community dwelling patients were requested for routine outpatient checkups at 6 weeks, 3 months and 1 year after surgery.

Prefracture institutionalized patients, or those not attending for any reason, had a checkup by phone, either with the patient, or an (in)formal caregiver.

Blood sampling and metabolic profiling

Residual blood from the routine venipuncture performed at the emergency department for preoperative blood work (EDTA plasma) was collected and stored for metabolic profiling by an external laboratory (Nightingale Health Ltd., Helsinki, Finland). The method for quantifying the metabolites using high-throughput NMR metabolomics has been described in depth previously.[26] The method provides simultaneous quantification of routine lipids, lipoprotein subclass profiling with lipid concentrations within subclasses, fatty acid composition, and low molecular metabolites, including amino acids, ketone bodies, and gluconeogenesis related metabolites, in molar concentration units. The technology has regulatory approval (CE) and 37 biomarkers have been clinically certified for diagnostic use. The obtained set of 272 metabolites includes the 14 used for the mortality risk score: total lipids in chylomicrons and extremely large VLDL (XXL-VLDL-L), total lipids in small HDL (S-HDL-L), mean diameter for VLDL particles (VLDL-D), ratio of polyunsaturated fatty acids to total fatty acids (PUFA/FA), glucose, lactate, histidine, isoleucine, leucine, valine, phenylalanine, acetoacetate, albumin and glycoprotein acetyls.[3]

Outcomes

The primary outcome of this study was patient survival, defined by the period between surgery (or admission for conservatively treated patients) and death due to any cause within 1 year.

The secondary outcome was the recovery of independence in ADL, which was defined as returning to the individual prefracture level of independence using the Katz ADL score assessed 6 weeks, 3 months and 1 year after treatment. Death due to any cause qualified as not returning to the individual prefracture level of independence, to avoid the otherwise consequential loss to follow-up.

Statistical analysis

Descriptive statistics are used to compare the patient characteristics and mean metabolite levels for patients who had and had not died. Means (with standard deviations, SD) are provided for continuous data with a normal distribution, and medians (with interquartile ranges, IQR) for data with a non-normal distribution (Kolmogorov-Smirnov test of $p < 0.05$).

The mortality risk score as constructed by Deelen et al. using the 14 sampled metabolites was calculated for each individual patient. This requires summing the weighted metabolites after log-transformation and scaling them (Appendix A).[3] Cox survival analyses were used to assess the association between the mortality risk score and survival, and the mortality risk score's association with the recovery of independence. The prediction accuracy of the mortality risk score was tested for mortality and the recovery of independence using a receiver operating characteristic (ROC) curve with the area under the curve (AUC).[27] This was tested for the mortality risk score by itself, and for the mortality risk score combined with the patients age and prefracture independence in ADL. The AUC was interpreted as follows: 0.9-1.0, excellent; 0.8-0.9, good; 0.7-0.8, fair; 0.6-0.7, poor; 0.5-0.6, fail.[28] Survival analyses were performed to assess the survival and recovery of patients for patients grouped into each tertile of the mortality risk score. Based on these outcomes, a potential cut-off value was explored using regression analyses for having a favorable survival outcome and recovery outcome. A p-value of <0.05 was considered statistically significant for all outcomes. All statistical analyses were performed using IBM SPSS statistics PC software version 25.0. The raw data and the analyses are available upon request.

Results

Complete data on the metabolomics and the characteristics age, sex, general health status, cognitive status and prefracture living situation were available from all patients. The remaining characteristics (prefracture mobility, independence in ADL and nutritional status) were complete for 126 (92.0%) patients.

The mean age of all patients was 82.1 years and the majority (68.5%) were female. Treatment was performed with an arthroplasty in 44.5%, with internal fixation in 53.3% and conservatively for 2.2% of patients.

Significant differences were observed for all baseline characteristics between patients who did and did not survive during follow-up, except sex and fracture type (Table 1). Of the metabolites, only S-HDL-L, VLDL-D, albumin and glycoprotein acetyls had different means for each group. There was a significant difference in the mean mortality risk score for patients who did and did not survive during follow-up (-0.097; SD, 0.62 and 0.42; SD, 0.87 respectively, P = 0.001). The distribution of the mortality risk score for each group (those who did and did not survive) is presented in Appendix B.

The median follow-up was 6 months (IQR 6) and 26 (19.0%) patients died within this period. The calculated mortality risk score ranged between -1.36 and 2.26.

Mortality

For every unit increase in this score, a 2.74 times higher mortality risk was observed in this cohort (HR, 2.74; 95% CI, 1.61-4.66; P < 0.001). The survival analysis indicates a 19.6% difference in the 1-year survival rate between patients from the highest and lowest tertiles, which was borderline significant (P = 0.049; Fig. 1). The biggest difference was observed between patients from the lowest tertile versus the medium and highest tertiles. This potential cut-off value (a mortality risk score of ≥-0.4055 or <-0.4055) yields a statistically significant hazard ratio of 2.99 (95% CI, 1.03-8.68; P = 0.044). The mortality risk score by itself showed a fair prediction accuracy for mortality (AUC = 0.68; 95% CI, 0.56-0.81). The model was enhanced to a good level of prediction accuracy when the mortality risk score was combined with the factors age and prefracture independence in ADL (AUC = 0.78; 95% CI, 0.68-0.88).

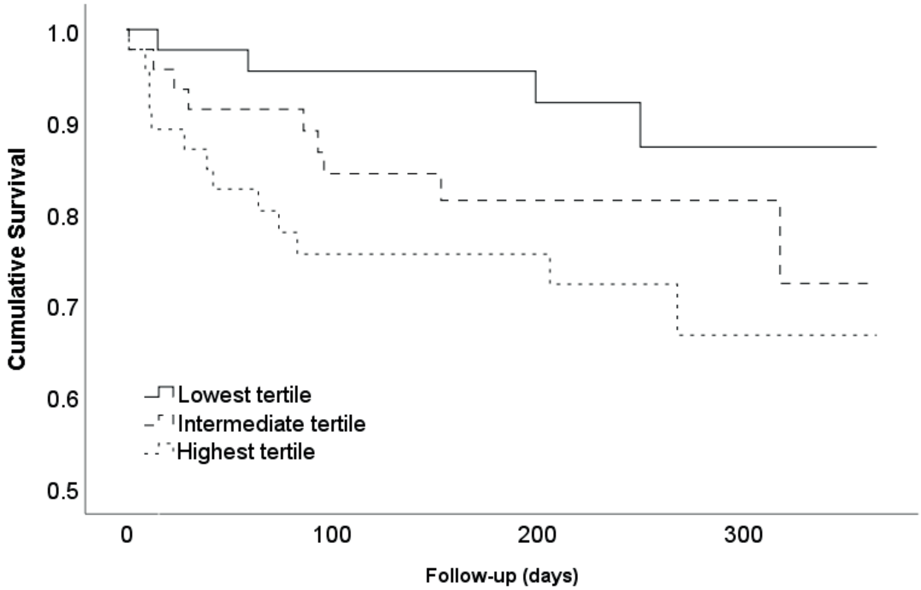
When results were stratified for fracture type, similar results were observed for both femoral neck fractures (HR, 2.88; 95% CI 1.23-6.74; P = 0.015; AUC = 0.72, Appendix Fig. C1a) and (sub) trochanteric fractures (HR, 2.61; 95% CI, 1.28-5.33; P = 0.009; AUC = 0.63, Appendix Fig. C1b).

Table 1. Baseline characteristics and metabolic profile for patients with a proximal femoral fracture.

Characteristic	Alive N=111 (81.0%)	Dead N=26 (19.0%)	P-value
Patient characteristic			
Age, y (SD)	81.0 (9.7)	86.8 (7.9)	*0.005*
Sex, f (%)	76 (68.5)	16 (61.5)	0.50
ASA classification (%)			
I-II	53 (47.7)	3 (11.5)	
III-V	58 (52.3)	23 (88.5)	*0.001*
Parker mobility score (%)			
7-9	57 (51.4)	2 (8.0)	
4-6	33 (29.7)	13 (52.0)	
0-3	21 (18.9)	10 (40.0)	*<0.001*
Katz ADL score (%)			
0-1	71 (64.0)	6 (25.0)	
2-3	16 (14.4)	6 (25.0)	
4-6	24 (21.6)	12 (50.0)	*0.002*
Cognitive impairment (%)	34 (30.6)	15 (57.7)	*0.010*
Malnourished (%)	46 (44.7)	17 (73.9)	*0.011*
Living situation (%)			
Independent	61 (55.0)	5 (19.2)	
Homecare or residential home	26 (23.4)	13 (50.0)	
Nursing home	24 (21.6)	8 (30.8)	*0.003*
Fracture type			
Femoral neck	62 (55.9)	12 (46.2)	
(Sub)trochanteric	49 (44.1)	14 (53.8)	0.372
Metabolic profiling*			
XXL-VLDL-L	0.18 (0.17)	0.16 (0.18)	0.63
S-HDL-L	1.08 (0.19)	0.93 (0.17)	*<0.001*
VLDL-D (nm)	37.97 (1.29)	37.41 (1.20)	*0.045*
PUFA/FA (%)	41.13 (3.01)	40.74 (3.56)	0.56
Glucose	6.66 (1.93)	6.61 (2.25)	0.91
Lactate	2.07 (0.88)	2.30 (0.85)	0.23
Histidine	0.06 (0.01)	0.06 (0.01)	0.74
Isoleucine	0.05 (0.02)	0.05 (0.02)	0.42
Leucine	0.09 (0.03)	0.08 (0.02)	0.66
Valine	0.20 (0.04)	0.19 (0.04)	0.13
Phenylalanine	0.05 (0.02)	0.06 (0.01)	0.36
Acetoacetate	0.08 (0.10)	0.07 (0.09)	0.56
Albumin (g/l)	35.77 (3.78)	33.38 (5.17)	*0.008*
Glycoprotein acetyls	0.88 (0.16)	0.97 (0.25)	*0.019*
Mortality risk score	-0.097 (0.62)	0.42 (0.87)	*0.001*

SD standard deviation, f female, ASA American Society of Anesthesiologists, ADL activities of daily living. * Means, concentrations are presented in millimole per liter (mmol/l) unless stated otherwise. nm nanometer, g/l gram per liter, XXL-VLDL-L Total lipids in chylomicrons and extremely large VLDL, S-HDL-L total lipids in small HDL, VLDL-D mean diameter for VLDL particles, PUFA/FA ratio of polyunsaturated fatty acids to total fatty acids. *Italics* indicate a P-value <0.05.

Figure 1. Survival curve of the overall survival stratified for the mortality risk score tertiles.



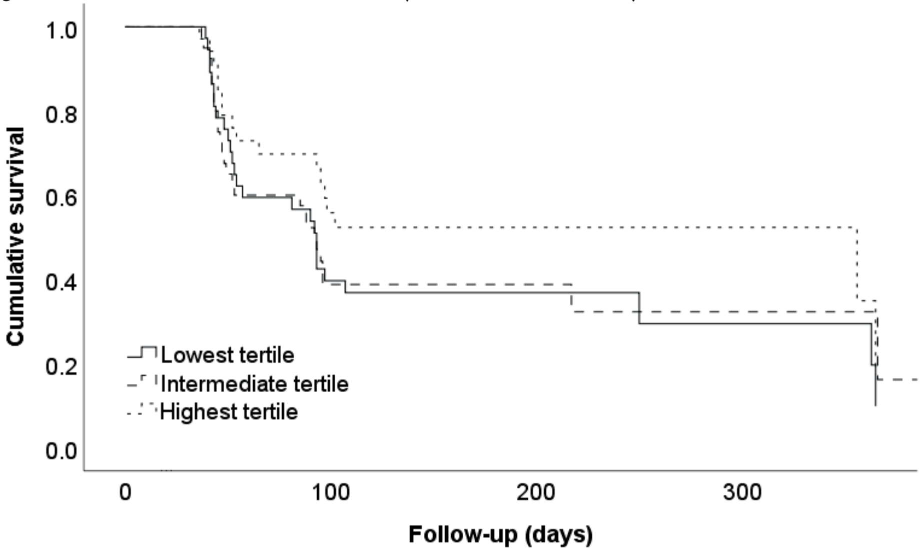
P = 0.049.

Recovery

Data on the independence in ADL was available for 132 (96.4%) patients. Of these, 70 (51.1%) recovered to their individual prefracture level of independence in ADL. No significant association was found between the risk of not recovering and the mortality risk score (HR, 0.72; 95% CI, 0.47-1.10; P = 0.1283) and although a 25.6% difference was observed in the recovery rate between patients from the highest and lowest tertiles, this was not statistically significant (P = 0.31; Fig. 2). Applying the potential cut-off value of the mortality risk score (≥-0.4055 or <-0.4055) to the functional recovery outcomes of patients yields no statistically significant hazard ratio (HR, 0.72; 95% CI, 0.47-1.10; P = 0.128). The tested predictive accuracy of the mortality score by itself indicated an AUC of 0.63 (fair) which enhanced after inclusion of the factors age and prefracture independence in ADL (AUC = 0.67; 95% CI, 0.58-0.76).

No significant results were observed when outcomes were stratified for the fracture types: femoral neck fractures (HR, 1.02; 95% CI 0.53-1.95; P = 0.95; AUC = 0.56, Appendix Fig. C2a) and (sub)trochanteric fractures (HR, 0.599; 95% CI 0.34-1.06; P = 0.077; AUC = 0.67, Appendix Fig. C2b).

Figure 2. Survival curve of the functional recovery stratified for the mortality risk score tertiles.



P = 0.31. Here, an event is defined as a patient recovering to their individual prefracture level of independence for activities of daily living.

Discussion

This preliminary study investigates the potential value of metabolomic profiling using a mortality risk score based on 14 metabolites to establish the mortality risk and recovery capacity of patients with proximal femoral fractures. These 14 metabolites have been associated previously with mortality in a range of EU population-based cohorts. A significant association with overall mortality and a borderline significant difference in the mortality rate of each tertile was found for the mortality risk score. The 2.74 times increased risk for mortality per unit increment of the mortality risk score corresponds neatly with the one found in the study of 11 EU cohorts (N = 44.000) by Deelen et al. (HR = 2.73).[3] In this study the predictive power of the score constructed on the basis of one (Estonian) study was validated in another (Finnish) cohort. In the validation, the AUC of the 5- and 10-year mortality was 0.84 and 0.83 respectively, which proved more effective than the predictive accuracy of models using conventional risk factors.[1, 3] The fair predictive accuracy of the mortality risk score reached in this study was much lower, but improved slightly when the conventional risk factors age and prefracture independence in ADL were added. The significant association between the mortality risk score and survival implies that metabolic profiling could potentially contribute to the prognostic accuracy in a model that combines both metabolomics and patient characteristics. The univariate study of each metabolite separately indicated that especially small HDL levels, the mean diameter for VLDL particles, albumin and glycoproteins differed significantly between the two groups. These markers have also been associated with cardiometabolic health and systemic inflammation. Small HDL and the mean diameter for VLDL particles are involved with lipid metabolism, and their regulation of plasma triglyceride is a potential risk factor for mortality.[29] Albumin and glycoprotein acetyls play an important role in inflammation.[30, 31] Although roles between the other metabolites included in the risk score and health have been described previously, their association with mortality could be explored more in-depth in future studies.[3]

The mortality risk score showed a more reserved association with a fair predictive accuracy for the recovery of independence in ADL. Although some of the metabolites in the score are related to the nutritional status, evidence on the relevance of the nutritional status and functional recovery in patients with proximal femoral fractures is limited.[20] Biomarker corresponding with functional outcome would represent the physical capacity to recover, which could be a construct of muscle status, endurance performance and metabolic health. However, aspects such as social support and self-determination might also play significant roles. Few studies have investigated these, possibly because they are harder to objectify than many other factors.[32]

Strengths and limitations

To our knowledge, this is the first study to attempt metabolic profiling in patients with a proximal femoral fracture.

Based on the patient characteristics this cohort seems representative of the average patient population. The number of patients included in this study was limited, and this sample size restricted the types of analyses that could be performed. As such, only age and prefracture functionality were added as covariates in multivariate models, purely to observe their effect on the accuracy of the model. A larger study with more patients should be used to validate the independent value of the mortality risk score, and could validate the findings of this preliminary study. Extensive validation should also be performed on the proposed cut-off value if it were to be applied in clinical practice.

The mortality risk score that was used in this study was designed to predict long-term survival in general populations. There are substantial differences between that population and the patients with a proximal femoral fracture. Patients with a proximal femoral fracture are exposed to significant excess mortality risks, with 1-year mortality rates between 20-25%.[7-9] This is substantially higher than the 12.5% mortality rate within the 2.76 years follow of the previous study by Deelen et al. in European cohort studies.[3] A risk score based on metabolites tailored for the patient population with a proximal femoral fracture only, could in theory be more effective. However, developing this would require a substantially larger number of patients.

The set of metabolites included in this study and all those investigated by Deelen et al., form only a fraction of all available metabolites in the human serum.[2, 3] Other sets of metabolites which have not yet been studied for these purposes could also prove more effective in predicting patient outcomes.

Conclusion

Although a modest prediction accuracy was observed for the mortality risk score in this population compared to those previously studied, the metabolomic profile assessed in this preliminary study is significantly associated with survival and aspects of it can potentially improve the prognostic accuracy for patients with a proximal femoral fracture. More elaborate studies are needed to develop a comprehensive model for clinical purposes.

Appendices

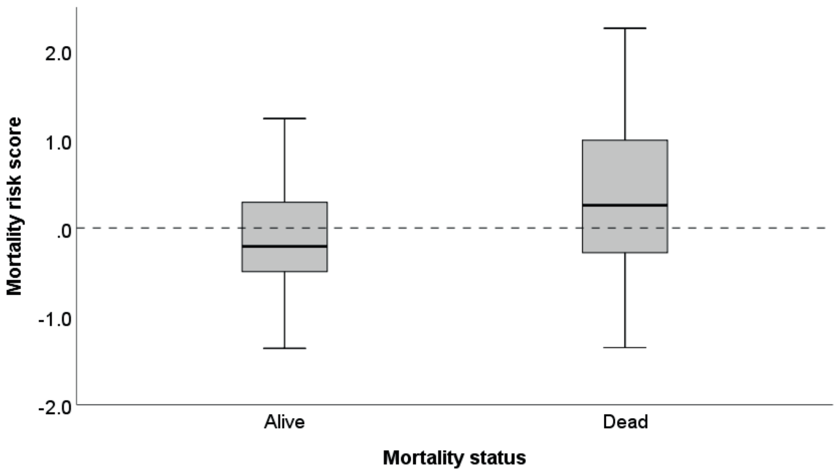
Appendix A

The mortality score as described by Deelen et al. was based on a study of the same metabolite platform as the current study but applied to 44.000 individuals indicating 136 highly correlated biomarkers out of 226 to be associated with mortality. A stepwise forward-backward regression procedure on the 63 (out of 226) least correlated markers revealed that 14 metabolites independently and significantly associated with mortality. The mortality score in the current paper, based on these 14 sampled metabolites, was calculated for each individual patient according to the procedure by Deelen et al. This requires summing the weighted metabolites after log-transformation and scaling them:

*Mortality risk score = (((Zln[XXL_VLDL_L])*ln(0.80)) + ((Zln[S_HDL_L])*ln(0.87)) + ((Zln[VLDL_size])*ln(0.85)) + ((Zln[PUFA_FA])*ln(0.78)) + ((Zln[Glucose])*ln(1.16)) + ((Zln[Lactate])*ln(1.06)) + ((Zln[his])*ln(0.93)) + ((Zln[Ile])*ln(1.23)) + ((Zln[Leu])*ln(0.82)) + ((Zln[Val])*ln(0.87)) + ((Zln[Phe])*ln(1.13)) + ((Zln[Acetoacetate])*ln(1.08)) + ((Zln[Albumin])*ln(0.89)) + ((Zln[GlycA])*ln(1.32))).*

Appendix B

The distribution of the mortality risk score for patients who did and did not survive.

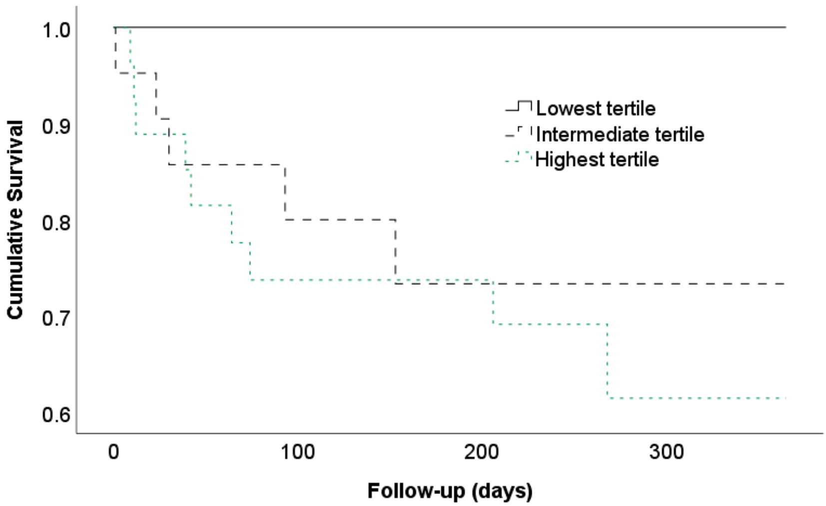


Mean score for no mortality: -0.097 (standard deviation, 0.62; range -1.36 to 1.67) and mortality 0.42 (standard deviation, 0.87; range -1.25 to 2.26), P = 0.001.

Appendix C

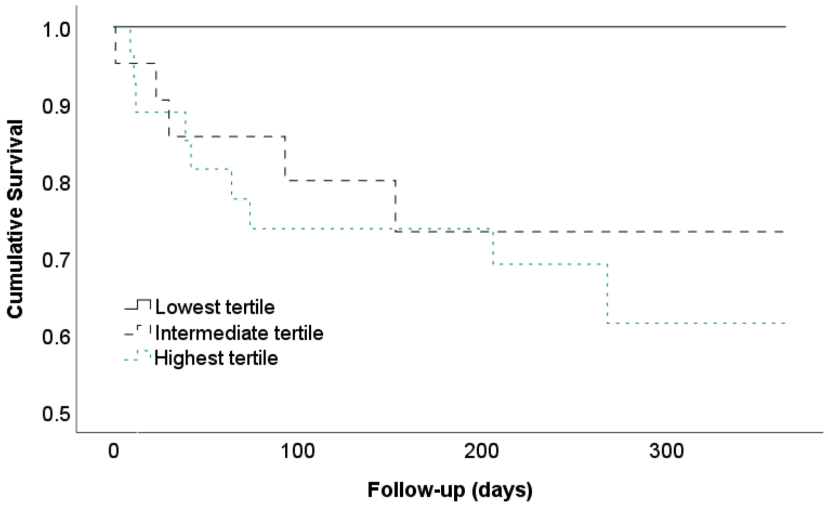
Survival curves of the overall survival and functional recovery, stratified for the mortality risk score tertiles and for each fracture type.

Appendix figure C1a. The overall survival for femoral neck fracture patients.



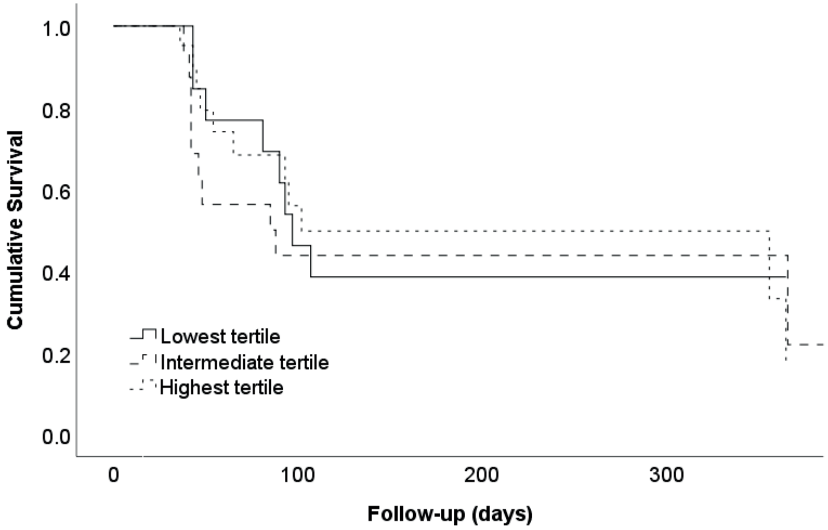
N = 63, P = 0.067.

Appendix figure C1b. The overall survival for (sub)trochanteric fracture patients.



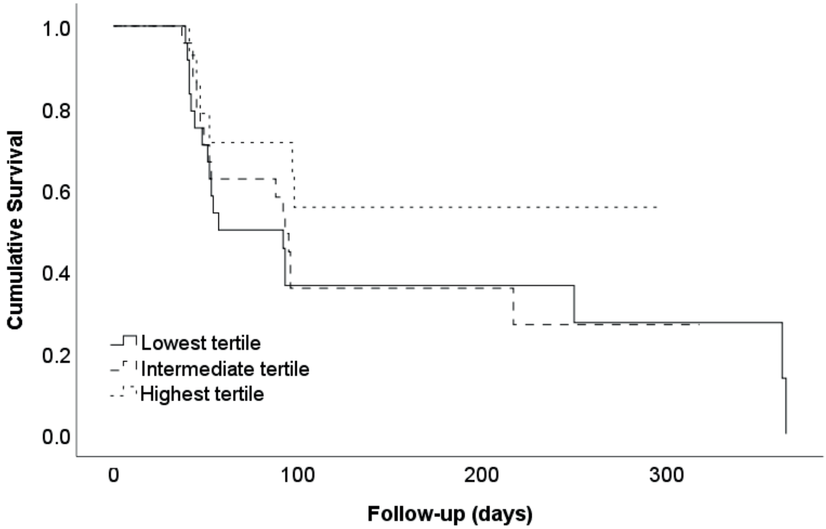
N=74, P = 0.59.

Appendix figure C2a. The functional recovery for femoral neck fracture patients.



N = 61, P = 0.93.

Appendix figure C2b. The functional recovery for (sub)trochanteric fracture patients.



N = 71, P = 0.33

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Chapter 9

General discussion

Proximal femoral fractures are severe injuries with major impact on the health status of older patients. Treatment and rehabilitation form a significant burden on the healthcare system, and even minor improvements in treatment aspects may prove beneficial for the patient survival and recovery. Such improvements are attempted through a multidisciplinary approach of care, with early involvement of geriatric specialists. Refined insight in the patients' health status and prognosis is valuable to determine treatment strategies and anticipate outcomes.[1]

This thesis aims to provide a better understanding of the factors relevant for the survival and functional prognosis of patients with a proximal femoral fracture. Proximal femoral fractures cause excess mortality and severe morbidity in the older population, and despite all efforts, little improvement has been observed in the past decades.[2] A better understanding of relevant factors could help to improve the outcomes.

Surgical approaches for arthroplasty (Chapter 2-3)

Improvement of the surgical techniques, implant types and the decision-making process for specific treatment options are the surgical efforts to reduce complications and improve functional outcome.[3, 4] Use of the anterior approach for arthroplasty in patients with a femoral neck fracture is an example of such an effort, as it is considered a less invasive technique compared to other conventional techniques.[5-8] Adaptation of this technique has been motivated by positive outcomes of the anterior approach in elective hip surgery. For these electively treated patients, the anterior approach seems favourable for early outcomes in terms of pain, rehabilitation time and outcome and length of stay.[9] These benefits could be especially favourable for older patients who are exposed to even higher risks for complications and loss of function compared to younger patients. Impairment of their postoperative mobility could result in the loss of independent living, which has major social and economic implications.

Our systematic review found several studies that looked at the functional outcomes of patients treated with a hemiarthroplasty via the anterior approach compared to other conventional approaches (*Chapter 2*).[10-15] Only few found significant differences, predominantly in short-term outcomes, compared to the lateral[11, 13] and posterior approach.[14, 15] Although these results suggest some advantages of the anterior approach, the lack of significant long-term differences may indicate that at most only a minor benefit can be expected. In contrast to the findings in elective hip surgery, effects of the surgical approach on long-term functional outcomes in this older patient population is likely to be diluted by other age-related factors. A meta-analysis of the functional outcomes of the different surgical approaches was not possible primarily due to the heterogeneity in the outcome assessments of all conducted studies.[16]

In the available literature on the surgical approaches for hemiarthroplasty, most studies focus primarily on the dislocation rate, and function was often only of the secondary outcomes, if studied at all.[12, 13, 17, 18] An implant dislocation is a major surgical complication and the foremost cause of reoperations and revisions.[16, 18] Our review confirmed favourability of the anterior approach compared to the posterior approach concerning the dislocation rate, but not for any of the other complications (including perioperative fractures and deep wound infections) or the reoperation rate compared to the posterior or lateral approach.[16, 19] In our own observational cohort study on the anterior and lateral approach, no benefits were observed for any of the complication rates including dislocations either (*Chapter 3*).

Despite the limited evidence on the benefits of the anterior approach, some findings concerning functional outcomes from elective surgery and proximal femoral fracture studies support each other. Better short-term functional outcomes could mean less need for walking aides, earlier recovered self-dependence, fewer admissions to geriatric rehabilitation (GR) centres or earlier discharge from GR centres. Even small contributions to such improvements would be beneficial for individual patients and for society.[11] But although such findings may be expected, they are currently not supported by literature.

A longer operation time and more surgical blood loss were observed for the anterior approach in our observational cohort study. This may indicate that the approach is technically more difficult. Intraoperative fractures have also been related to the difficulty in exposing and manipulating the femur during femoral stem preparation in elective hip surgery.[9] This risk may be even higher in the more osteoporotic bone of older patients with a proximal femoral fracture. Articles on the learning curve of surgeons report a minimum of 25 to 100 operations required to sufficiently reduce the incidence of such complications and the operative time.[20, 21] This is a substantial amount, especially for trauma surgeons in the Netherlands who miss experience from elective hip surgery in contrast to orthopaedic surgeons. Even in high volume centres, most trauma surgeons won't reach the required level of experience within one year. These challenges are probable obstacles for surgeons to make a transition to the anterior approach, and would explain why each approach has retained its popularity for patients with a proximal femoral fracture.

Prognostic factors of functional recovery (Chapter 4-8)

While the evidence on the effects of different surgical techniques on the functional outcomes of patients with a proximal femoral fracture treatment is limited, our systematic review presents numerous other factors that have been associated with function (*Chapter 5*). Factors that have been identified by multiple studies on proximal femoral fracture patients with sufficient levels of evidence include age, comorbidity, cognition and prefracture functionality.

Some overlap of factors was observed for resilient patients who reached independent living within 3 months after treatment (*Chapter 6*). For these patients, the factors age and cognition did not indicate a significant relevance for further recovery of independence. Fear of falling was a factor included by few previous studies that indicated a significant relevance in this study also.[22]

A notable factor for which no decisive evidence was found in both of our studies was the nutritional state. Our study on malnutrition screening tools showed a high prevalence of malnutrition in this patient population (*Chapter 4*). A poor nutritional status has previously been associated with adverse outcomes such as mortality and complications,[23-28] but the association with functional outcome has been elusive.[29] Different tools are used to assess the nutritional status, and studies using the MNA-SF more often indicate a significant associations with functional outcome than others (*Chapter 5*).[26, 30-34] The reason for this could be because the MNA-SF also includes assessments of mobility, cognition and general health to assess the risk of malnutrition.[35]

Some biomarkers associated with the nutritional status, have in some cases been associated with functional outcome.[32, 36, 37] The mortality risk score by Deelen et al. (2019) is a score based on a set of biomarkers including some nutritional metabolites, and was constructed to predict long-term mortality in general populations.[38] The score showed a significant association with mortality in our studies, but did not indicate a significant association with recovery (*Chapter 8*). Whether the mortality risk score has an independent prognostic value in this patient population, while adjusting for other of the previously identified prognostic factors, remains to be tested. Construction of a recovery prediction model based on a set of biomarkers tailored for this patient population could be attempted, as there might still be a prognostic value of biomarkers other than those in the mortality risk score.

A wide range of other factors have been included by very few studies. These include, anaemia, pain, depression and vitamin D.[29, 37, 39] For most of these factors, studies have concluded differently on their prognostic value and the size of the effects. Consequently, the overall level of evidence for these factors has been deemed low.[29] Significant heterogeneity has been observed in the methodology of the studies in our and previous reviews, which might explain how different studies conclude differently.[29] The methodological discrepancies seem often caused by subtle differences in study goals, subjective choices associated with those goals as well as with organizational challenges.

The discrepancies between studies highlight a number of important methodological dilemmas. The definition and method of assessment of each factor is of prime importance, as is exemplified previously by our study on the nutritional status (*Chapter 4*). No single definition for each factor is perfect, as each has been created and applied with a specific intent. Many of the tools and assessments used in the prospective observational studies of this thesis (*Chapter 3*, *6* and *8)* were selected for their validity and frequency of use in previous studies concerning patients with a proximal femoral fracture. This enhances the comparability of outcomes, but as demonstrated in our systematic review (*Chapter 5*), many of these tools have similar alternatives, such as the Katz ADL and the Barthel index (for activities of daily living), the MNA-SF and the MUST (for malnutrition) and the ASA classification or CCI (for comorbidity). While similar and used with the same intentions, namely to assess specific patient characteristics, variation in the type of assessments used may lead to variations in the independent associations of factors and the outcome measure of prognostic models.

Another explanation is that studies handled different patient selection criteria. Some of our own studies of functional outcome (*Chapter 6* and *Chapter 7*) focussed specifically on prefracture community dwelling patients. We argue that for these patients, who generally have no severe cognitive or physical impairments, the social and economic implications of functional decline are substantial, as they risk losing autonomy, privacy and independency.[40-42] In addition, adequate outpatient follow-up of these patients is more feasible and less burdensome than for institutionalized patients who are frequently cognitive impaired. Even for community dwelling patients, adequate follow-up in routine outpatient settings is challenging due to the patient's severe comorbidities, cognitive decline, impaired mobility and frequent dependency on caregivers. This makes the study of functional outcome much more complex and strenuous compared to other outcomes and to other patient populations. The use of questionnaires, which is also possible by phone, is much more attractive than physical assessments at outpatient check-ups or home visits in larger cohort studies.

Use of questionnaires has another benefit compared to physical assessments. Studies either assess absolute functional outcome in absolute measures, or the relative functional recovery to the individuals own prefracture level of function. In young, healthy patient populations, patients generally aim to recover to an absolute level of unimpaired function, which usually corresponds to their prefracture state. In contrast, the prefracture functionality varies substantially among older patients, as most of these patients already experienced some degree of functional impairment before the occurrence of the fracture.[43-45] Consequently, recovery to the maximal functional level is relatively rare and can't be expected from the majority of these geriatric patients.[44, 45] For older patients, successful recovery might be defined more accurately according to their individual prefracture functional status. This was pursued by the use of a combined outcome measure (*Chapter 6-8*). A major limitation to the application of this method arises from the nature of the injury. The patient's individual prefracture functionality and mobility can only be assessed retrospectively via (hetero)anamnesis after the fracture has occurred.[46] This baseline assessment is the essential reference standard for the patient's individual recovery. This method would thus not be feasible when using physical performance assessments such as the FAC, SPPB or TUG scores.

Recovery to an individual prefracture level of function may also be considered a more patient-centred outcome.[47] Prognostic models based on such an outcome, such as the ones discussed in *Chapter 6*, allow for predictions on the chances for a specific patient to recover sufficiently to return to independent living, or to their prefracture level, at different moments in the recovery process.

A disadvantage of using an absolute measure of functional outcome, rather than assessing the recovery to an individual's prefracture level, is the consequential loss to follow-up in case of mortality. Workarounds opted by few studies is to categorize the assessment of function and allocate deceased patients to the unfavourable outcome group[37, 48], or to use post-mortem interviews with a proxy, to retrospectively assess function close before death.[49] Another novel solution is the use of multi-state modelling, as these models allow for the inclusion of any potentially competing events such as mortality (*Chapter 6)*. In addition, it can be used more flexibly to determine the patients prognosis at different stages of the recovery process.[50]

Of the articles reviewed in *Chapter 5*, the majority studied the patients' functional outcomes in absolute terms. A perfunctory comparison of the outcomes regarding prognostic factors identified by these studies and by the studies that looked at the patients' return to individual prefracture levels of function, however, indicated no major differences were observed.

Another important source of heterogeneity in the findings of different studies on prognostic factors, is the method of handling covariates. The prognostic value of a factor is determined by the association found between each factor and the outcome while adjusting for potential confounding factors using multivariate analyses. Many different models composed of sets with different factors have been studied. Very few of these models with a fixed set of well-defined factors have been applied and validated by more than one study. Limitations in the definitions of specific factors, and the composition of the sets in which they are used, highlight another limitation in determining their prognostic value.

Many factors tend to be a construct of more fundamental, biological factors, and these constructs may overlap. A suitable example of this is the most powerful prognostic factor: age. While chronological age is a proxy for biological age, biological age is simply a construct representing the heterogeneity in health and life expectancy. Biological age can be constructed using any combination of any number of assessments on health. These may include diagnosed medical conditions, measures of frailty, functional status, nutritional parameters, metabolic markers[51, 52], or factors associated with senescence such as genomic instability, DNA methylation[53, 54], stem cell exhaustion, telomere attrition and loss of proteostasis.[55] Similarly, a factor such as the functional status might be a construct of muscle mass, muscle strength, respiratory capacity, functional impairments (such as neuromuscular pathology or arthralgia) and motivational or cognitive problems.[56-58] This causes a circular logic that undermines comparisons of different prognostic factors using models with different sets of prognostic factors; Because of the underlying constructs, any factor in a model is likely to influence the effects of all other factors in that model. This also highlights the importance of adjusting for other major factors when assessing the independent association of a factor with an outcome. It also explains heterogeneity in the findings of different models, more specifically how contradicting conclusions can be formed on the prognostic value of specific factors, such as the nutritional status.[31, 33, 37, 59]

While one strategy towards an accurate model may be to select the most fundamental prognostic factors, such as biomarkers, this may not form a practical model useful in clinical settings. An alternative goal would be to construct a convenient applicable model using well-defined, easily obtainable factors, such as those already in use for routine care (that include age, sex and comorbidity scores), or a combination of both using biomarkers assessed using blood from routine perioperative tests.

Interpretation of the findings on factors relevant for the functional prognosis of patients with a proximal femoral fracture has been challenging. This field of research is characterized by little homogeneity in the methodology of different studies. Factors that seem relevant for virtually all versions of functional outcome and most subgroups of patients with proximal femoral fractures are general health status based on comorbidity and prefracture functionality. This highlights the importance of a holistic and geriatric approach in patients with proximal femoral fractures. Surgical aspects may be of importance for surgical complication rates, but is evidently outweighed by the relevance of patient characteristics for long term functional outcome. This warrants close examination of patients and endorses the importance of post-acute multidisciplinary GR. Loss of function and independence have major social and economic consequences, and this patient population is at high risk of acute functional decline.

We have suggested a novel analysis using multi-state modelling and a composite outcome to study recovery, which defines three aspects of independency, these being the return to prefracture levels of independence in ADL, the return to independent living, and survival. It can be used to assess whether patients have returned to their individual prefracture level of independence. This outcome is patient-centred and seems feasible in routine care settings.

Future perspectives

Epidemiology

The WHO has estimated a drastic increase in the population fraction aged 65 years and more, for whom the risk of osteoporotic fractures is highest, over the coming decades. This ageing of the world population can be attributed to improved socioeconomic stability, availability of healthcare, preventative medicine and an increase in medical interventions that prolong life expectancy.[60-62] The change in the populations' age distribution means that the global number of osteoporotic fractures including proximal femoral fractures will probably increase.[63-65] However, the age-specific incidence of proximal femoral fractures seems to decline over the last decade[64-66] and national incidences tend to plateau in some of the more developed countries.[67, 68] This indicates that the majority of the global increase in osteoporotic fractures can be expected in low and middle income countries. Predictions based on extrapolated incidences and their associated costs from historic data, do tend to ignore future progress in the prevention and treatment of osteoporosis.[69]

Treatment

Treatment for patients with a proximal femoral fracture didn't go much further than fracture surgery for a long time. Only in recent decades has the relevance of multidisciplinary care for these patients become more mainstream. This has led to the new standard of having orthogeriatric hip fracture units in developed countries.[70, 71] Further centralization of care in even more specialized centres may help to improve clinical expertise, efficiency and ultimately the outcomes even more.[72] Treatment protocols may become more comprehensive, including details on the post discharge rehabilitation. This forms the basis of a better post-acute chain of care, including treatment agreements with physiotherapy clinics, GR homes and nursing homes.

Conservative fracture treatment for the frailest patients with severe cognitive and functional impairments may become more accepted, as the focus of treatment shifts towards quality of life and the apprehension for palliative care increases amongst healthcare specialists and relatives.[73, 74] Increased prognostic accuracy would significantly aid the shared decision-making process for the frailest patients.

Further development of implant types for osteosynthesis and arthroplasty as well as improvements in the surgical techniques may reduce the surgical complication risks and improve patient outcomes. Such improvements, however, will most likely have only a reserved effect on the functional outcomes of patients.

Research

Our study group will continue with the ongoing HIP CARE study (*Chapter 7*), which focusses on a few complex factors. The nutritional state is assessed in addition to muscle strength and muscle mass, to study the mutual relationships and effects on recovery. Social aspects and mood are also assessed during the recovery process. In addition, the study of serum metabolites and their independent prognostic value for mortality and function in this population will continue, to test the independent prognostic value.

Future research on prognostics in general would do well to define clear aims on how the knowledge obtained would be applied for clinical purposes. For example, research focused on the prognostic value of nutritional status could simultaneously study which patients would be most cost-effective candidates for interventional programs with nutritional supplements or additional physiotherapy.

Alternatively, prognostic models of functional recovery may also be used to shape patients' and physicians' expectations, act as an early post-acute care needs assessment, and help to plan care accordingly. This could mean arranging assistance in ADL for patients who are expected to lose independency, or planning discharge from rehabilitation centres when recovery is expected to stagnate. A prognostic model could be implemented in clinical care pathways, where the prognosis of patients is evaluated at fixed intervals after surgery and displayed real-time in a medical dashboard. Multi-state modelling allows input of new data gathered during the rehabilitation process which adjusts the predicted outcomes at these fixed intervals (which could correspond with routine outpatient visits and assessments).

Such models should be extensively validated, but as demonstrated in *chapter 5*, few prognostic models from studies on patients with proximal femoral fractures have been validated in later studies. This is in contrast to various other fields of medicine, such as stroke.[75] Future studies may want to focus on multinational validations of developed prognostic models that have well-defined clinical implications. It is questionable, however, if sufficient levels of accuracy can be achieved for ever changing health systems with numerous subtle differences.

Improvements may be driven by current developments in the field of big data science. Machine learning methods are potentially more successful in producing algorithms to accurately predict patient outcomes upon admission than more traditional methods that have been exploited so far.[76-78] Currently, prognostic research tries to find an accurate or workable model by assimilating a set of patient characteristics. Alternatively, a prognostic algorithm could be designed using machine learning with not just a set of characteristics, but all clinical data available. Machine learning has been applied in prognostics for a wide range of medical topics.[79-81] The effectiveness of such a model, however, depends very much on the size and comprehensiveness of the data input.

Currently, much more clinical data is collected per patient, than is being used in research. Mostly because it is not formatted in a desirable way, or because the abundancy of data is overwhelming for the study design. Obtaining vast datasets for retrospective observational multicentre studies remains challenging, as the type and method of the routine data collection is not synchronized between different hospitals. Consequently, the data can't be merged easily into a single database. National registries such as the Dutch Hip Fracture Audit of the Netherlands, the National Hip Fracture Database of England and Norwegian Hip Fracture Register of Norway enforce registration of data in a homogenous way and could provide extensive uniform datasets on routinely collected patient and treatment characteristics.[82-84] Currently, much of this data collection is performed through double registrations by staff of the healthcare institutes. This makes it workable only for a very limited set of routine hospital data. While automatization of this process is being developed in collaboration with the electronic health record companies at time of writing, it again only applies to the limited set of routine hospital data. Further synchronization of healthcare data collection would ultimately improve the potentials in this extensive field of research. It would require substantial efforts to reach consensus on the methods to assess the patients prefracture health status and the methods to assess outcomes.

Besides homogenization of the data collection for hospitals, other healthcare providers could also participate. This would stimulate a more 'chain-of-care' approach, with easier exchange of homogenous patient data. Patient background information from general practitioner or nursing home records could be valuable during the admission of patients, and these healthcare providers may more accurately record long-term patient outcomes, including functional outcomes. Adequate follow-up of functional outcomes for older patients has proven to be very challenging in current routine outpatient settings.[82] Additional benefits for the clinical processes of free data exchange between healthcare providers are obvious. However, at least in the Netherlands, working towards a national electronic health record has so far proven to be problematic due to extensive privacy concerns.[85]

To improve the estimation of the functional decline attributed to proximal femoral fractures in older patients, future studies could focus on excess functional decline. This would give a more valid estimation of the adverse effect on functionality and the additional burden for society of proximal femoral fractures besides mortality. Excess mortality is a major outcome in fields of research where the studied pathology might not be the sole risk of mortality. In older patients with a proximal femoral fracture, the relevance of excess mortality is obvious, as mortality rates in the general population at age 80 (the mean age of patients with a proximal femoral fracture) is about 5% .[86, 87] Similarly, significant functional decline may be expected in the general older general population too. The vast majority of people lose their independence and mobility, requiring homecare or admission to a nursing home, in their latest stage of life.[88] In fact, many disorders that may have induced the fall and subsequent fracture, (such as joint pain associated with degenerative arthropathies, cardiovascular disorders, neurological disorders including Parkinsonism or diabetic neuropathy and impaired vision) are likely to progress with age.[89] The progression of these comorbidities will by themselves cause further functional decline and form a competing risk for functional outcome. As such, it may be more interesting to address excess functional decline in this older population rather than functional decline as an absolute measure. Excess functional decline would represent the functional decline directly attributed to proximal femoral fractures and treatment. As in excess mortality, case and control groups must have very similar health statuses with as little differences in comorbidity ratings as possible (other than the fracture) to determine the excess decline most accurately. Such studies have not yet been conducted in patients with a proximal femoral fracture, or any other field of medical research. Consequently, the current understanding on the true potential therapeutic gain in function and independence by improved care in this population is limited.

Promising areas of research have been highlighted, and new entry points have been presented. Further progress in the improvements of clinical outcomes for patients with a proximal femoral fracture, however, will take tremendous efforts. Optimising the cooperation between all healthcare specialists involved in the treatment and rehabilitation of these frail patients is of the utmost importance here.

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Summary

Proximal femoral fractures (often denoted as hip fractures) are amongst the most prevalent fractures in older patients. These fractures are associated with significant mortality and morbidity. Failure to recover to prefracture levels of function has important social and economic implications, as these patients risk losing their independence and self-reliance. Prognostication is of clinical importance as it helps to determine treatment strategies. Interventions could be developed and applied for modifiable risk factors of adverse outcomes. Alternatively, non-modifiable factors are important for the prognostic accuracy, which helps to shape expectations and steer advance care planning. The enormous heterogeneity in the health status of older patients makes prognostic efforts very challenging.

The primary aim of this thesis is to provide a better understanding of the factors relevant for the functional prognosis of patients with a proximal femoral fracture.

This thesis covers two parts which focus on the effects of surgical aspects and patient demographics. The studies presented in part one describes the different surgical approaches for arthroplasty in femoral neck fractures. Part two includes studies which focus on the methods to assess patient demographics and their relevance towards functional outcome.

In *Chapter 2* a meta-analysis compares the outcomes of the three major surgical approaches for hemiarthroplasty in patients with a femoral neck fracture, these being the anterior approach (AA), lateral approach (LA) and posterior approach (PA). Each is considered a viable approach for routine care with no consensus on the superiority of one. Twenty-one eligible studies, comparing at least two of these approaches, were included. A significantly higher risks of dislocations for the PA was indicated. No significant differences were found concerning perioperative fractures, wound infections, and hospital length of stay. Only limited and heterogenous data was available on the functional outcomes of each approach. Some studies suggest a better short-term functional outcome using the AA compared to the PA, but this was not conclusive.

In *Chapter 3*, a prospective observational cohort study compares the application and surgical outcomes of the AA with the LA. Both approaches are routinely used for arthroplasty in the study hospital. Significant differences were observed in the baseline characteristics of patients treated with the AA and LA, mostly associated with the more frequent use of THA in the AA group. The overall incidence of surgical complications was 7.8% and 8.1% for the AA and LA respectively and did not differ significantly. A significantly longer operation time and more blood loss was observed for the AA, but this was not considered clinically relevant or confirmed by the majority of previous studies.

Two screening tools routinely used during admission of acute medical patients, the SNAQ and MNA-SF were compared in a cross-sectional study to assess their screening capacity the ESPEN

criteria as the golden standard of the nutritional status (*Chapter 4)*. The negative effects of malnutrition are well studied, including its effect on the outcomes of hip fracture surgery. The prevalence is considered very high in this older patient population, and further deterioration of the nutritional status can be provoked by factors associated with acute care and a lengthy rehabilitation process. In this study 16.9% of all patients was diagnosed as malnourished by the ESPEN criteria and 20.1% to 47.8% were classified as either at risk for malnutrition or as malnourished by the SNAQ and MNA-SF respectively. A moderate agreement was found between the tools (k = 0.68), and while the SNAQ was proven to be a very specific screening tool, 28.4% of all malnourished patients with a proximal femoral fracture had a false negative outcome. Consequently, no benefits were observed for the SNAQ over the MNA-SF, as consequent under treatment of fragile older patients should be avoided.

In a systematic review which included 31 studies on the independent factors associated with long-term functional outcome, thirteen factors were studied (*Chapter 5)*. The current understanding of prognostic factors of functional recovery after a proximal femoral fracture is limited, and enhancements could improve the prognostic accuracy and target subgroups for additional care strategies. Of the studied factors, only age, comorbidity, functionality and cognition had a substantial level of evidence supporting a significant effect. The remaining factors (including residence and social status, ethnicity, psychological status, nutritional status, vitamin D, fracture type, delay in surgery and complications) had not. None of the available data could be pooled due to the enormous heterogeneity in the definition of successful recovery and the methods to assess patient demographics. This highlights one of the major challenges in this field of research.

The study described in *Chapter 6* is a prospective observational cohort study of community dwelling patients, and their transitions through different states of the recovery process. A multi-state model was used to define each state and transition, which enables visualization of the population phasing from treatment to their final endpoint. Of all patients, 65.5% returned to independent living with recovered levels of independence in ADL within the 3-month follow-up. Factors that were deemed significantly associated with a successful recovery of independence for patients who succeeded to return to independent living, included: general health status, prefracture mobility, prefracture independence and fear of falling. Factors including cognition, nutritional status and anaemia were not. Novel applications of the multi-state model are suggested for further studies.

Chapter 7 describes the design of a prospective observational inception cohort study including premorbid community dwelling patients with a proximal femoral fracture. The aim of the study is to identify independent prognostic factors of functional recovery with an emphasis on the nutritional status and sarcopenia using handgrip strength and fat-free mass index assessments. Functional recovery is defined using a composite outcome of the patient's survival, living situation and individual functional recovery assessed at 6 weeks, 3 months and 1 year after surgery.

In *Chapter 8*, the prognostic value of a previously constructed mortality risk score, composed of 14 biomarkers, is tested on a cohort of patients with a proximal femoral fracture with a median follow-up of 6 months. Within this period, 19.0% of all patients died, and 47.7% returned to prefracture levels of independence in ADL. The mortality risk score, originally designed for general populations with a long-term follow up, had a significant association with mortality in this population also (HR, 2.68) and a fair prediction (AUC = 0.682). No such association was observed between the mortality risk score and functional recovery of patients. Although the potential for prognostic value was observed, more elaborate studies are needed to validate these findings and to develop a comprehensive model for clinical purposes.

Although some benefits of the anterior approach have been observed concerning the complication rate and functional, mayor clinically relevant differences such as better or shorter recovery are lacking. There are substantial barriers to adopt the surgical approach, with a shallow learning curve and risks of peroperative complications.

Interpretation of the findings on factors relevant for the functional prognosis of patients with a proximal femoral fracture has proven to be challenging. This field of research is characterized by little homogeneity in the methodology of different studies. Factors which seem relevant for virtually all versions of functional outcome and most subgroups of patients with proximal femoral fractures are comorbidity and prefracture functionality. This highlight the importance of a holistic and geriatric approach in patients with proximal femoral fractures. This warrant close examination of patients and endorses the importance multidisciplinary rehabilitation. Loss of function and independence have major social and economic consequences, and this patient population is at high risk.

We have suggested a novel composite outcome to study recovery, which defines three aspects of independency, these being the return to prefracture levels of independence in ADL, the return to independent living, and survival. It can be used to assess whether patients have returned to their individual prefracture level of independence. This outcome is patient-cantered and seems feasible in routine care settings.

Samenvatting

Een proximale femur fractuur (ook wel heupfractuur genoemd), is een ernstige breuk die veel voorkomt bij ouderen. De breuk is sterk geassocieerd met hoge risico's op mortaliteit en morbiditeit. Slecht herstel van de functie na deze breuk heeft belangrijke sociale en economische gevolgen, omdat deze patiënten daarmee hun zelfstandigheid en zelfredzaamheid verliezen. Prognostiek heeft een groot klinisch belang, aangezien dit kan helpen bij het bepalen van het behandelplan. Interventies zouden ontwikkeld en toegepast kunnen worden op veranderlijke risicofactoren geassocieerd met een slechte uitkomst. Anderzijds zijn onveranderlijke risicofactoren interessant voor de prognostische nauwkeurigheid. Deze helpen om verwachtingen te schetsen en te anticiperen op toekomstige zorgbehoeftes. De enorme heterogeniteit in de gezondheidsstatus van oudere patiënten met een proximale femur fractuur maakt prognostiek een uitdagende opgave.

Het primaire doel van dit proefschrift is om de factoren die relevant zijn voor de functionele prognose van patiënten met een proximale femur fractuur beter te begrijpen.

Het proefschrift is opgedeeld in twee onderdelen die gericht zijn op chirurgische aspecten en demografische patiëntgegevens. Deel I bevat studies die verschillende chirurgische benaderingen voor het plaatsen van een heupprothese bestuderen. In deel II richten studies zich op methodes om functieherstel te bestuderen, en wordt onderzocht welke factoren er relevant zijn voor deze uitkomst.

In *Hoofdstuk 2* wordt in een systematische review met behulp van meta-analyses de uitkomsten van drie veel gebruikte chirurgische benaderingen vergeleken in patiënten met een proximale femurfractuur. Dit zijn de anterieure benadering (AB), de laterale benadering (LB) en de posterieure benadering (PB). Elk van deze wordt beschouwd als een gangbare chirurgische benadering die routinematig wordt gebruikt, zonder consensus onder artsen of een van deze superieur is ten opzichte van de anderen. Eenentwintig geschikte studies die ten minste twee van deze benadering met elkaar vergeleken werden geïncludeerd. Een significant hoger risico op dislocaties werd geobserveerd voor de PB. Er werden geen andere significante verschillen geobserveerd in de incidentie van perioperatieve fracturen, wondinfecties en duur van de ziekenhuisopname. De data betreffende functionele uitkomstmaten van iedere benadering was zeer gelimiteerd en heterogeen van aard. Sommige studies waren suggestief voor een beter korte-termijn herstel in functie voor de AB vergeleken met de PB, maar dit werd niet als doorslaggevend beschouwd.

In *Hoofdstuk 3* vergelijkt een prospectieve observationele cohortstudie de toepassing en de chirurgische uitkomsten van de AB met de LB. Zowel de AB als de LB wordt routinematig gebruikt voor prothesiologie in het studie-ziekenhuis. Er werden significante verschillen geobserveerd in de karakteristieken van patiënten die werden behandeld middels de AB en de LB, wat voornamelijk geassocieerd was met het vaker gebruiken van een totale heupprothese in de AB-groep. De incidentie van chirurgische complicaties was 7.8% en 8.1% voor de AB en LB respectievelijk, en verschilde niet significant van elkaar. Een significant langere operatieduur en meer bloedverlies werd geobserveerd voor de AB, maar dit werd niet klinisch significant geacht of ondersteund door de meeste andere, eerder uitgevoerde studies.

De negatieve effecten van ondervoeding zijn goed bestudeerd, alsmede de effecten ervan op de uitkomsten van heupfractuur chirurgie. Twee meetinstrumenten voor ondervoeding die routinematig werden gebruikt voor acuut opgenomen patiënten, de SNAQ en MNA-SF, werden met elkaar vergeleken in een dwarsdoorsnedeonderzoek waarbij de ESPEN-criteria dienden als de gouden standaard voor de voedingsstatus (*Hoofdstuk 4)*. De prevalentie bleek relatief hoog in deze oudere patiëntenpopulatie, en verdere verslechtering van de voedingsstatus kan worden uitgelokt door factoren geassocieerd met acute zorg en het langdurige revalidatieproces. In deze studie werden 16.9% van alle patiënten ondervoed bevonden volgens de ESPEN-criteria, en 20.1% tot 47.8% geclassificeerd als risicopatiënten voor ondervoeding of ondervoed door de SNAQ-score en MNA-SF respectievelijk. Slechts een matige overeenkomst werd gevonden tussen de twee meetinstrumenten ($k = 0.68$), en terwijl de SNAQ-score een erg specifiek meetinstrument bleek, kregen 28.4% van alle ondervoede patiënten met een proximale femurfractuur een vals-negatieve uitkomst. Zodoende werden er geen voordelen gevonden van de SNAQ-score ten opzichte van de MNA-SF, omdat onderhandeling van kwetsbare oudere patiënten vermeden dient te worden.

In een systematische review waarin 31 studies over onafhankelijke factoren geassocieerd met lange-termijn functionele uitkomsten werden geïncludeerd, werden 13 individuele factoren bestudeerd (*Hoofdstuk 5)*. De huidige kennis van prognostische factoren van functioneel herstel na een proximale heupfractuur is gelimiteerd, en verdere ontwikkeling hiervan zou de prognostische accuraatheid kunnen verbeteren en subgroepen kunnen selecteren voor additionele zorginterventies. Van de bestudeerde factoren werden alleen leeftijd, comorbiditeit, functionaliteit en cognitie doorslaggevend geacht met een afdoende niveau van bewijs. De overige factoren (woonomgeving, sociale status, etniciteit, psychologische status, voeding status, vitamine D status, fractuurtype, vertraging tot de operatie en complicaties), hadden onvoldoende bewijs. Vanwege de enorme heterogeniteit in de definitie van succesvol herstel en de methodes om de factoren te beoordelen was het niet mogelijk om de data samen te voegen voor verdere analyses. Dit karakteriseert een van de grote beperkingen en uitdagingen in dit onderzoeksgebied.

Hoofdstuk 6 betreft een observationele studie met prefractuur zelfstandig wonende patiënten, waarbij gekeken werd hoe zij verschillende fases van herstel doorlopen. Hier is gebruik gemaakt van een multi-state model waarin verschillende fases en transities tussen deze fases zijn gedefinieerd. Dit helpt om het herstelproces van de gehele populatie te visualiseren en te bestuderen. Van alle patiënten kwam 65.5% terug op hun oude niveau van zelfstandigheid en zelfredzaamheid binnen de 3-maanden tijdsduur van deze studie. Factoren die significant geassocieerd waren met succesvol herstel, voor de patiënten die een zelfstandige woonomgeving bereiken, zijn comorbiditeiten, prefractuur mobiliteit en functionaliteit, en valangst. Onder de factoren die niet geassocieerd waren vallen cognitie, voeding status en anemie. Het toepassen van multi-state modellen bleek nieuwe kansen voor innovatieve analyses te bieden die het herstel van patiënten beter in kaart brengt.

Hoofdstuk 7 beschrijft een studieontwerp voor een prospectief observationele cohortstudie voor prefractuur thuiswonende patiënten met een proximale femurfractuur. Het doel van deze studie is het identificeren van onafhankelijke prognostische factoren met de nadruk op de voeding status en sarcopenie welke beoordeeld worden met behulp van de handknijpkracht en vetvrije massa metingen. Functioneel herstel wordt gedefinieerd als een composiet uitkomst bestaande uit de overleving, de woonsituatie en het herstel van functie naar het individuele prefractuur niveau van de patiënt gemeten op 6 weken, 3 maanden en 1 jaar na de operatie.

In *Hoofdstuk 8* wordt de prognostische waarde van een eerder ontwikkelde mortaliteitsrisico score, die bestaat uit 14 biomarkers, getoetst in een cohort van patiënten met een proximale femur fractuur. In de mediane duur van 6 maanden overleed 19.0% van alle patiënten, en herstelde 47.7% naar het prefractuur niveau van zelfstandigheid. De mortaliteitsrisico score, die ontwikkeld is voor algemene populaties die voor een lang termijn worden gevolgd, vertoonde een significante associatie met de mortaliteit in deze populatie (HR, 2.68) en een redelijke voorspelbaarheid (AUC = 0.682). Een dergelijke associatie werd niet gezien voor de mortaliteitsrisico score en de kans op herstel van patiënten. Alhoewel er potentie gezien werd voor de voorspellende waarde van de mortaliteitsrisico score, moeten uitgebreidere studies dit nog valideren. Alleen dergelijke studies kunnen hier een model van maken met klinische toepassingen.

Concluderend lijken chirurgische aspecten zoals de benadering voor het plaatsen van een prothese een terughoudende rol te spelen in de functionele uitkomsten van patiënten met een proximale femur fractuur. Het bewijs voor betere functionele uitkomsten hiermee lijkt marginaal, en klinisch relevante verschillen ontbreken. Tegelijk is er een hoge drempel om de nieuwe techniek te leren.

De uitkomsten van verschillende studies naar factoren die relevant zijn voor de functionele prognose van patiënten laat zich moeilijk interpreteren. Er is een hoge mate van heterogeniteit in de methodologie van deze studies. Factoren die zeker wel relevant lijken in verreweg de meeste onderzoeken en subpopulaties, zijn gezondheidsscores op basis van de comorbiditeiten en het prefractuur functioneren. Dit benadrukt het belang van een holistische en geriatrische aanpak bij patiënten met een proximale femurfractuur. Het motiveert het goed in kaart brengen van de patiënt tijdens de behandeling, en een multidisciplinaire aanpak tijdens de revalidatie. Onvolledig herstel en een verlies van zelfredzaamheid hebben grote sociale en economische gevolgen, en deze patiëntenpopulatie vormt een uitgesproken risicogroep.

In dit proefschrift wordt een innovatieve samengestelde uitkomst gepresenteerd voor het bestuderen van functieherstel. Hierbij wordt gekeken naar drie cruciale aspecten, namelijk de overleving, terugkomst in een zelfstandige woonomgeving en het herstel van zelfstandigheid bij activiteiten van het dagelijks leven. Dit is een patiëntgerichte uitkomstmaat die goed toepasbaar lijkt in de kliniek.

Appendix

Data collection of the HMC Hip Fracture Centre

Routine collection of data in the external coded database on patients with a proximal femoral fracture for the HMC Hip Fracture Centre stared on the 20th December 2016. Data was collected prospectively, simultaneously with the hospital record, on a wide variety of patient characteristics, treatment aspects and outcomes of all patients admitted to the emergency departments of the HMC. This data was recorded in a database of Castor EDC, a program which enables researchers to easily capture and integrate high-quality data from any source on one compliant platform. The data was used for periodic hospital checks on the quality of care and the outcomes of minor clinical interventions, the national data registrations including the DHFA, the LROI, the ZiN and IGJ, and for scientific research.

Appendix table A-I. Overview of the HMC Hip Fracture Centre data registration.

During admission			**During follow-up**
Patient characteristics	**Admission details**	**Fracture treatment**	**At 6w, 6m, 1y**
Sex	Transfer from other hospital	Treatment type	Residency
Age	ED admission time	Time to surgery	Pain (NRS)
Comorbidity (ASA)	Hospital length of stay	Duration of surgery	Pain medication use
Prefracture residency	Pain (NRS)	Surgeons experience level	Complications**
Hb level	Pain medication use at ED and discharge	Anaesthesia type	Frequency of physiotherapy*
Fracture type (AO)	Delirium risk		Functionality
Comorbid fractures	Delirium score		PMS*
Previous hip fractures	DOS scores		Katz ADL
Cognition	Complications**		HHS
6CIT	Discharge location		FAC
Diagnosed dementia			SPPB
Frailty assessment			TUG
Fall Risk			Quality of life (EQ-5D, NRS)
Delirium risk			Cognition (6CIT)
Active smoker			Fear of Falling (FES-i7)
Prefracture functionality			
Katz ADL			
PMS*			
Nutritional status			
BMI			
SNAQ			
MNA-SF			
Fear of falling			

*Since 2018, ** Postoperative bleeding, hematoma formation, mechanical implant failure, implant dislocation, femoral head osteonecrosis, periprosthetic fracture, reoperation, superficial wound infection, deep wound infection, nerve damage, other (surgical), anaemia, congestive heart failure, myocardial infarction, cardiac arrythmia, cerebrovascular accident, pressure ulcer, delirium, electrolyte disturbances, gastro-intestinal bleeding, ileus, obstipation, gastro-intestinal ulcer, COPD exacerbation, pulmonary embolism, pneumonia, respiratory insufficiency, mortality, kidney failure, sepsis, deep venous thrombosis, phlebitis, urinary tract infection, urinary retention, new fall without fracture, new fall with fracture, other (non-surgical).

List of abbreviations

6CIT	Six Item Cognitive Impairment Test
AA	Anterior Approach (also: direct anterior approach, DAA)
ADL	Activities of Daily Living (also: Katz ADL index)
AO	Arbeitsgemeinschaft für Osteosynthesefragen (Association for the Study of Internal Fixation) fracture classification
APACHE	Acute Physiology, Age, Chronic Health Evaluation score (see also: APS)
APS	Acute Physiological score of APACHE II (see also: APACHE)
ASA	American Society of Anesthesiologists Classification
BDRS	Blessed Dementia Rating Scale
BI	Barthel Index
CCI	Charlson Comorbidity Index (also: Charlson Index (score), CI)
CES-D	Centre for Epidemiologic Studies Depression Scale
CIRS-G	Cumulative Illness Rating Scale - Geriatric
CRP	C-Reactive Protein
DASH	Disabilities of the Arm, Shoulder and Hand Score
DHFA	Dutch Hip Fracture Audit
ESPEN	European Society of Clinical Nutrition and Metabolism
FAC	Functional Ambulatory Categories
FFMI	Fat Free Mass Index
FIM	Functional Independence Measure
FNF	Femoral Neck Fracture
FRS	Functional Recovery Scale
GDS	Global Deterioration Scale
GR	Geriatric Rehabilitation
HA	Hemiarthroplasty
HR	Hazard ratio
HET	High Energy Trauma (also: major trauma)
HFC	Hip Fracture Centre
HGS	Handgrip Strength (also: handgrip force, HGF)
HHS	Harris Hip Score
HIPCARE	Hip fractures: Inventarisation of Prognostic factors and their Contribution towArds Rehabilitation in older pErsons
IADL	Instrumental Activities of Daily Living (Lawton-Brody)
LA	Lateral Approach (also: straight lateral approach, SLA)
LROI	Landelijke Registratie Orthopedische Implantaten (Dutch Registry for Orthopaedic Implants)

MADRS	Montgomery–Åsberg Depression Rating Scale
MCS	Mental Component Score (of the SF-12/SF-36)
MMSE	Mini–Mental State Examination test
MNA	Mini Nutritional Assessment (LF Long Form, SF Short Form)
NRS	Nutrition Risk Screening (2002)
PA	Posterior Approach (also: posterolateral approach, PLA)
PCS	Physical Component Score (of the SF-12/SF-36)
PFF	Pertrochanteric Femur Fracture
PS	Propensity Score
RAND	RAND comorbidity score (also: SF-36)
RFG	Relative Functional Gain
SBT	Short Blessed Test (also: Orientation-Memory-Concentration Test)
SD	Standard Deviation
SF-12	12-Item Short Form Survey
SF-36	36-Item Short Form Survey (also: RAND)
SNAQ	Short Nutritional Assessment Questionnaire
SPMSQ	Short Portable Mental Status Questionnaire
THA	Total Hip Arthroplasty
TT	Tinetti Test
TUG	Timed Up and Go test
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index (also: LCF WOMAC, functional domain of the WOMAC score)

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Curriculum vitae auctoris

The author of this thesis, Max Paschalis Ludo van der Sijp, was born on the 7th of April 1991 in Blaricum, the Netherlands. He grew up with his parents and older brother in Weesp and Hilversum. After graduation from the International School Hilversum in 2009 and a gap-year abroad, he started studying medicine at the University Leiden (Leiden University Medical Centre) in 2010.

During his studies he enjoyed traveling abroad including internships at the Kanti Children hospital Kathmandu in Nepal and the Jaja Dande Hospital Djoemoe in Surinam, as well as high-altitude mountaineering trips. He also participated in oncological research on colorectal cancer with prof. dr. R.A.E.M. Tollenaar at the department of surgery in the Leiden University Medical Centre from 2011 onwards.

In 2015, during his surgical internships at the Haaglanden Medical Centre, he started studying the outcomes of proximal femoral fracture surgery with dr. A.H.P. Niggebrugge and Prof. dr. I.B. Schipper. A comprehensive care-pathway and prospective database were constructed and developed further in collaboration with the department of Old Age Medicine of the Haaglanden Medical Centre (dr. M. van Eijk) and the department of Public Health and Primary Care of the Leiden (prof. dr. W.P. Achterberg).

After his graduation with honours as bachelor of medicine in 2014 and master of medicine in 2017 he worked briefly as a surgical resident at the Haaglanden Medical Centre, where he had also completed his ‘dedicated schakeljaar’. He then started as a full-time researcher at the department of Public Health and Primary Care of the Leiden University Medical Centre to work on his thesis, supervised by his promotor prof. dr. W.P. Achterberg. Simultaneous with his clinical research, he contributed in the steering committee for proximal femoral fractures at the Haaglanden Medical Centre and helped with the national data registrations.

During his last few months of full-time research, he also worked night- and weekend shifts as a surgical resident. This period coincided with the start of the COVID-19 pandemic. By summer 2020, Max returned working as a surgical resident, this time at the Leiden University Medical Centre. He currently lives in the city centre of the Hague with his beloved partner, Wiesje.

PhD portfolio

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	Dr. J.H. Hegeman

PhD Training

General courses

Good Clinical Practise Landsteiner Institute	2015
Introductory meeting Promovendi University Leiden	2018
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2018
Basic methods and reasoning in Biostatistics	2018

Specific courses

Bot cursus Delft	2018
ESSETS course LUMC	2018
Boerhave statistics course 'Analysis of Repeated Measurements'	2019
AO Trauma Course 'Fragility Fractures and Orthogeriatrics'	2020

Regional conferences

TOWN ('Trauma Overleg West-Nederland')	2017-2020
Project market LUMC campus the Hague	2018, 2019
Symposium 'Op weg naar betere geriatrische revalidatie'	2018
Wetenschapsdag LUMC	2018
HMC wetenschapsmiddag (oral presentation)	2018

National conferences

Traumadagen NVT	2017

Traumadagen NVT (oral presentation)	2018
Chirurgendagen NVvH	2018
Chirurgendagen NVvH (oral presentation)	2019
Traumadagen NVT (poster presentation, 2x)	2019
National debate 'datadilemma's in de zorg'	2019

International conferences

EuGMS congress (poster presentation)	2019

PhD Teaching

Lecturing

Boerhaave training 'Orthopedie en Revalidatie'	2018
Wetenschapsavond Ouderengeneeskunde	2018
Landelijke Keuzedag Verdieping Somatiek SOON	2020

Tutoring

Workgroup 'Patient-partner GRZ'	2019
Workgroup 'Trauma of the Extremities'	2019

Additional training and courses

E-learning Nza 'medisch-specialistische zorg'	2018
E-learning 'Registratie aan de bron'	2019
Masterclass 'Registratie aan de bron'	2019
E-learning WBG 'The Future of Work: Preparing for Disruption'	2019
Webinar 'Dokteren in de digitale wereld'	2020
Webinar 'AI in de zorg'	2020

Ancillary activities

Data collection and reporting for the HMC Hip Fracture Centre, the taskforce 'hip fracture infections' and the national data registries DHFA and LROI.	2016-2020