PREDICTORS OF OUTCOME IN HIP FRACTURE PATIENTS

Sophie Moerman

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Hip fractures are a rising problem in our aging society. Although age-adjusted hip fracture incidence has decreased in some parts of the world, like the United States, other parts, like Asia, have seen an increase in age-adjusted fractures. [1] The reason for this geographically bounded decrease in hip fractures is unclear, but it might be explained by the rise in bisphosphonate treatment and increasing obesity. [1] However, the protective role of obesity in osteoporosis is debated, and the compliance with bisphosphonate treatment is limited. [2, 3] In Europe, the age-adjusted incidence of hip fracture is stable, and the total population is not expected to increase in the next 25 years. However, the proportion of elderly aged more than 85 years will increase by 129% for men and 73% for women, and this will lead to an increase in the incidence of hip fractures in Europe to 815,000 in 2025 (+32%). [4, 5] Worldwide, an increase to 21 million hip fractures in 2050 is expected. [4]

Mortality after a hip fracture is high: the one-year rate is approximately 23%. [6] Despite many technological developments, this mortality rate has been stable for the last 30 years. [6]The 3-month mortality rate is five to eight times higher than the mortality of matched patients without a hip fracture. [5]

Patients who survive the sequelae of a hip fracture will have significant loss of function. Not only is mobility diminished in the direct post-operative period, but a large fraction (30-90%) of surgically treated patients still had reduced mobility at one year after the hip fracture treatment. [7–9] Basic functioning and more advanced functions, such as self-care and household tasks, are also reduced dramatically after a hip fracture. [10] The consequent loss of independence will result in more need for health care resources such as long-term rehabilitation and may even lead to permanent dependence on nursing home facilities. [11]

Morbidity and mortality after hip fractures can be expressed as loss of quality-adjusted life years (QALYs). Hip fractures led to 600,000 lost QALYs in Europe in 2010. [5] In the Netherlands, hip fracture care costs are 445 million euros per year. This is about 27 euros per person per year. These costs are expected to increase 30% by 2025. [5]

Current scientific insights and gaps

For frail hip fracture patients, it is of great importance to provide early surgical care without later need for re-intervention. For decades, there has been debate on how to improve hip fracture surgery. In 1935, the terminology ‘unsolved fracture’ had already been linked to a hip fracture by Kellog Speed, reflecting the complexity in

treatment outcomes depending on patient factors, fracture characteristics and surgeons' preferences. [12]

A treatment shift from internal fixation of the fracture towards arthroplasty has occurred in recent years. Arthroplasty can reduce the incidence of major complications and re-operations compared to internal fixation. [13–16] Furthermore, it provides better pain relief and function. [13] However, arthroplasty is not suited for all kinds of hip fractures, and surgeons require specific expertise for specific fracture types. The American Academy of Orthopedic Surgeons (AAOS) and National Institute for Health and Care Excellence (NICE) guidelines advise arthroplasty in displaced intracapsular hip fractures. [17, 18] The Dutch guidelines advise physicians to consider internal fixation in displaced hip fractures in healthy patients younger than 80 years who are able to undergo a revision and in patients who are immobile. For all other patients, arthroplasty is the preferred treatment. [19]

Another ongoing debate is when a total hip arthroplasty (THA) or a hemiarthroplasty (HA) is indicated in hip fracture patients. Guidelines are ambiguous on this topic. NICE advises use of THA instead of HA in patients who walk with no more than the use of a stick, have good cognition and are medically fit for anaesthesia, while the Dutch guidelines advise physicians to consider internal fixation for this patient group. [18, 19]A few randomised controlled trials have been performed in recent decades; they showed no difference in the revision rate of HA and THA. [20, 21] Another debated topic in hip fracture surgery is whether the stem should be cemented or not. [22, 23]

Numerous attempts have been made to reduce the high complication rate in the frail hip fracture patient population. Important progress on patient outcomes has been made through better collaboration between surgical and geriatric/internal medicine staff. Orthogeriatric care covers a range of different forms of combined care, from geriatricians to orthopaedic (trauma) surgeons. [24] The exact content of orthogeriatric care differs per hospital and has changed over time. General guidelines have been set forth, but the individual components of this care should be evaluated more closely. [18] The next step would be to provide orthogeriatric care that is tailor-made for patients. In order to provide this individualised care, we must be able to identify patients who would benefit more from a specific component of care than other patients. Identifying risk factors and developing prediction models will help health care providers deliver high-quality care within budget.

Aim of this thesis

The first goal of this thesis is to evaluate how to minimize the risk of re-operation when performing arthroplasty surgery in frail elder hip fracture patients. We will mainly focus on whether cement should be used when placing a stem.
The second goal is to identify, at an early point in time, patients at risk of poor outcomes, including mortality, post-operative delirium, large loss of health-related quality of life (HRQoL) and large loss of instrumental activities of daily living ((i) ADL).

Outline of the thesis

This thesis has two parts. The first part is on outcome of arthroplasties in hip fracture patients, and the second on predicting outcomes in hip fracture patients.

Part I: (Hemi) arthroplasty

Intracapsular hip fractures can be treated with internal fixation or arthroplasty. In recent decades, a shift towards arthroplasty has taken place, because it leads to fewer complications, fewer re-operations, better pain relief and superior function. [13] In this part of the thesis, we will focus on performing arthroplasty with the smallest chance of re-intervention.

Risk factors for re-intervention

The landelijk Register Orthopedische implantaten (LROI) is the Dutch nationwide population-based register with data on joint arthroplasties. Register studies have certain advantages compared to cohort studies; the number of included patients is high, and if there is no selection bias, they are representative of real-world data. In **Chapter 2**, we will explore revision rates of hip fracture patients after both HA and THA. We will analyse LROI register data of 30,830 patients treated with arthroplasty for acute hip fracture and will perform a risk analysis for revision in this patient group. We will include type of stem fixation and type of approach as possible risk factors in the analysis.

Cemented versus uncemented hemiarthroplasty

Both NICE and AAOS guidelines advise the use of cemented implants. [17, 18] Despite these guidelines, database studies show that 22 to 34 % of hemiarthroplasties are performed without cement. [25, 26] Fear of bone cement implantation syndrome (BCIS), a reaction characterised by hypoxia and/or hypotension in combination with an unexpected loss of consciousness that occasionally occurs following cement insertion, makes some surgeons hesitant

to use cement. [27] A Cochrane review on cemented and uncemented stems did not show a difference in mortality but did find that patients with cemented stems had less pain, better function and fewer complications. In **Chapter 3**, we describe a randomised controlled multicentre trial in which 201 patients with displaced hip fractures were randomised between cemented and uncemented HA.

Part II: Predictors of mortality, delirium, quality of life and daily life functioning after a hip fracture

Hip fractures have an enormous impact on the lives of the elderly patients involved. The societal and economic impacts of a hip fracture are also substantial; medical costs for hip fracture patients are approximately twice as much as those for an age- and residence-matched control population without a hip fracture. [28, 29] Because health care is becoming more expensive and the number of hip fractures will rise, it is important to target care. [1] This is only possible if we can predict which patients will recover without any extra intervention (such as physiotherapy, nutritional supplements, etc.), which will recover with an additional intervention, and which will not recover despite this additional intervention.

Mortality

The mortality rate after a hip fracture is high, with an average 30-day mortality of approximately 10%. [30]Orthogeriatric care can likely reduce this mortality rate, but its cost-effectiveness is uncertain. [31, 32] Being able to identify patients with the highest risk of mortality will help target this expensive care appropriately. The Nottingham Hip Fracture Score (NHFS) was designed to identify the patients at the highest risk of mortality. [33] In the Netherlands, a new mortality-predicting score based on this NHFS was designed with better predictive properties. [34] In **Chapter 4**, we used our cohort of hip fracture patients to perform an external validation of this new score and to compare it to the NHFS.

Delirium

Delirium is a common and serious complication in hip fracture patients. It is characterised by a disturbance in attention and awareness and a change in cognition that develops over a short period of time and fluctuates during the day. [35] Reported post-operative incidence rates range widely, from 16 to 62%. [36] Delirium leads to decreased functional abilities, longer hospital stays, impaired cognitive function, more admissions to long-term special care facilities and higher mortality rates. [37–40]

Haloperidol as prophylaxis
Haloperidol is an antipsychotic drug that is widely used for treating the symptoms of delirium once it occurs. In 1999, Kaneko showed that use of haloperidol as a prophylaxis reduced the incidence of delirium after gastrointestinal surgery. [41] However, a larger randomised trial with hip fracture patients could not reproduce these findings. [42] In 2008, we started to treat patients at high risk of delirium with prophylactic haloperidol. In **Chapter 5**, we measured the incidence of post-operative delirium and compared it with the incidence prior to 2008.

Identifying patients with high risk of delirium
Some interventions, such as bispectral index (BIS)-guided anaesthesia and multi-component interventions, are capable of reducing incidence of post-operative delirium. [43] To properly target these interventions, it is important to identify patients at a high risk of delirium. This risk assessment should be simple and brief to increase participation of both patients and medical professionals. In Chapter 5, we describe the risk model for delirium (RD) score, which was developed in our hospital based on common risk factors, and we describe the use of the score in daily practice. In **Chapter 6**, we describe the clinical reliability, validity and feasibility of the RD in hip fracture patients.

Quality of life
Health-related quality of life (HRQoL) is an individual's or a group's perceived physical and mental health over time. [44] Although this perceived health is different for each individual, instruments such as SF-12 and EQ5D have been developed to measure HRQoL. [45] **Chapter 7** describes a prospective cohort study with 335 hip fracture patients. In this cohort, we tried to find risk factors for decline of HRQoL after a hip fracture.

Daily life functioning
Daily life functioning can be divided into two categories, activities of daily living (ADL) and instrumental activities of daily living (iADL). Activities of daily living are self-care activities (such as dressing), and iADL are activities necessary for independently living in a community (shopping, preparing meals). Functional decline can lead to a lower quality of life for patients and higher costs for society (as more institutionalised care or domestic help is required). [46, 47] Therefore, it is important to identify patients who will experience more decline in function after a hip fracture. For that purpose, we evaluated the (i)ADL of 480 hip fracture patients in our prospective cohort, and the results are described in **Chapter 8**.

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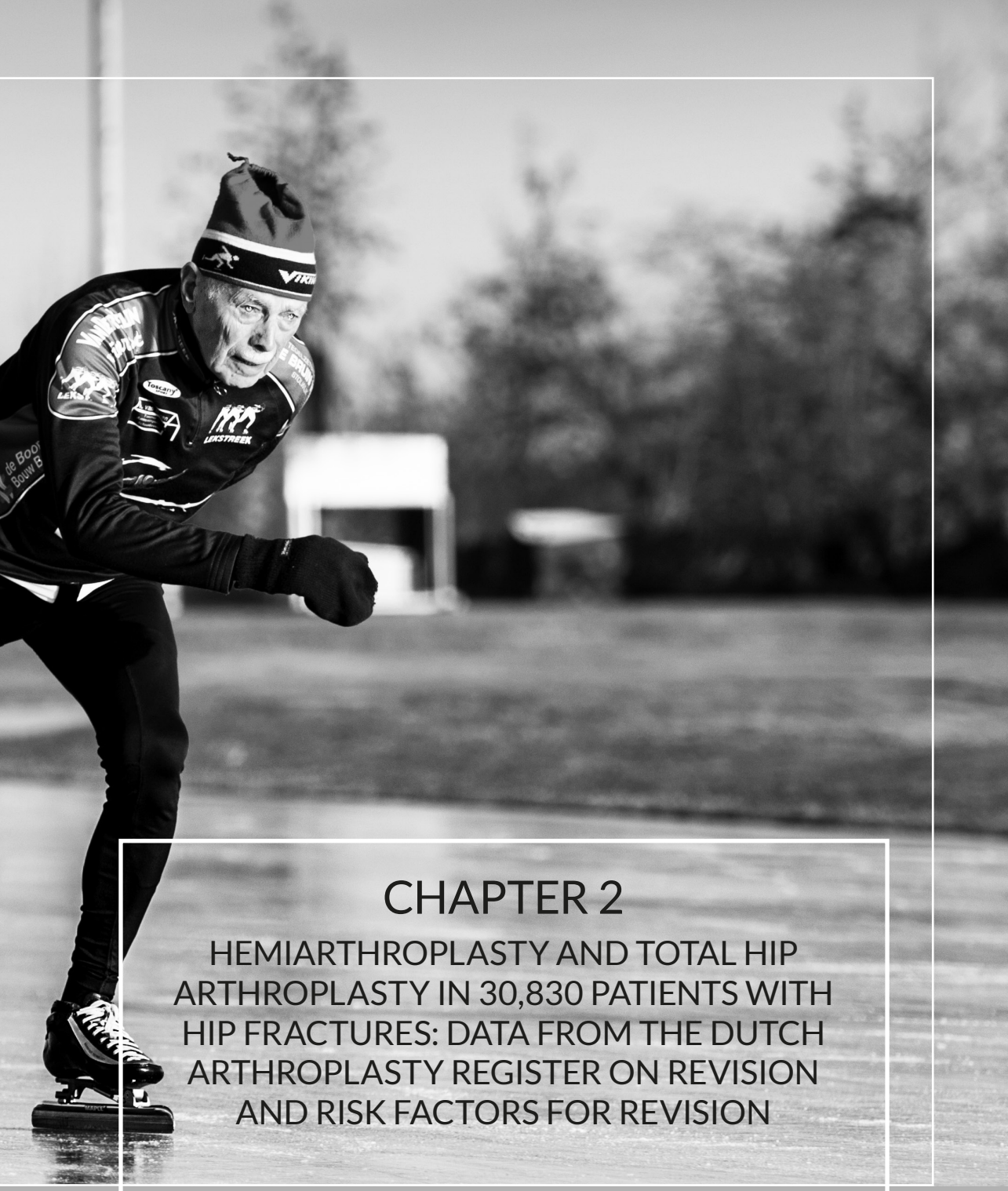

CHAPTER 2

HEMIARTHROPLASTY AND TOTAL HIP ARTHROPLASTY IN 30,830 PATIENTS WITH HIP FRACTURES: DATA FROM THE DUTCH ARTHROPLASTY REGISTER ON REVISION AND RISK FACTORS FOR REVISION

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Abstract

Introduction

In the Netherlands about 40% of the hip fractures are treated with a hemiarthroplasty (HA) or a total hip arthroplasty (THA). Although these procedures are claimed to have less complications than osteosynthesis (i.e. reoperation), complications still occur. Analyses of data from national registries with adequate completeness of revision surgery are important to establish guidelines to diminish the risk for revision. We identified risk factors for revision.

Methods

All patients older than 50 years of age with a hip fracture treated with arthroplasty by orthopedic surgeons and registered in the (national) Dutch arthroplasty register (LROI) were included in the study. In this register, patient characteristics and surgical details were prospectively collected. Revision surgery and reasons for revision were evaluated. A proportional hazard ratio model for revision was created using competing risk analysis (with death as competing risk).

Results

1-year revision rate of HA was (Cumulative Incidence Function (CIF) (95% CI)) 1.6% (1.4 - 1.8) and THA 2.4% (2.0 - 2.7). Dislocation was the most common reason for revision in both groups (HA 29%, THA 41%). Male sex, age under 80 years, posterolateral approach and uncemented stem fixation were risk factors for revision in both THA and HA. THA patients with ASA classification III/IV were revised more often, whereas revision in the HA cohort was performed more often in ASA I/II patients.

Conclusion

When an arthroplasty is indicated in hip fracture patients, both a posterolateral approach and an uncemented hip stems have higher risks for revision surgery.

Introduction

Arthroplasty surgery for acute hip fractures is performed in large numbers worldwide. In the Netherlands about 21,000 hip fractures occur annually. [1] In about 40% of these cases a hemi-(HA) or total hip arthroplasty (THA) is used. [2] Although these latter procedures are claimed to have less complications than osteosynthesis of the fractured hip, complications still occur. [3] Analysis of observational data from national registries will give more readily data which can be of clinical value, but such studies are rare. [4–6] A meta-analysis demonstrated a lower risk of reoperation and better function after THA compared to HA [7], a more recent review found comparable outcomes between (bipolar) HA and THA. [8] None of these studies used national registry data. Also other issues like the use of a cemented or an uncemented stem, an unipolar or a bipolar HA and what surgical approach is best to use, still remain open. [4, 9, 10] Therefore, we performed an analysis into failure mechanisms (i.e. endpoint revision surgery and reasons for revision) of hemiarthroplasties and total hip arthroplasty using data from the national Dutch Arthroplasty Register (LROI)

Methods

All acute hip fractures treated with a HA or a THA by orthopedic surgeons that were registered in the LROI between 2007 and 2017 were included in the study. Patient characteristics (sex, age at procedure, ASA classification, smoking and BMI) and surgical details (approach, type of fixation and type of implant) are prospectively registered. [11] All records in the LROI are linked by the encrypted citizen service number unique to each Dutch inhabitant. All revision operations during which components are replaced as well as reasons for revision are also registered into the database. The citizen number allows to link these revisions to the primary procedure. Reason(s) for revision surgery are coded in the database with multiple response variable set: dislocation, peri-prosthetic fracture, infection, loosening femoral component, loosening acetabular component, cup / liner wear and other reasons.

For this study we included all registered patients older than 50 years of age, treated with a THA or HA for an acute hip fracture. The LROI has a completeness for primary THA (independent of indication for THA) of 98%, and 88% for revision arthroplasty. [11] The completeness of primary HA augmented from 70% in 2013 to 88% in 2015. [12, 13] In the Netherlands, HA for hip fracture is performed by both orthopedic and trauma surgeons, THA for acute fractures is performed only by orthopedic surgeons. As the registration in LROI by trauma surgeons only started

in 2014 and completeness is low, patients treated by trauma surgeons are not included in the current study.

Statistics

Baseline characteristics for THA and HA are compared with a Student's t-test for continuous variables and the Chi Square test for categorical variables. We considered differences between groups to be statistically significant if the P values were less than 0.05.

The high risk of mortality after arthroplasty surgery is an important competing risk for revision operations. Due to the effect of the competing risk (in this case death) there is a chance of potential under- or overestimation of incidence of reoperations using a Kaplan-Meier analysis. [5, 14, 15] If, for example, an uncemented prostheses in this study was applied to a healthier population with a lower incidence of death, the probability of revision would be higher for that group. For this reason competing risk analysis was performed with STATA 11.2 using the Cox model [16]. The estimated Cumulative Incidence Functions (CIF) for revision are presented in graphs for both THA and HA. These CIFs were compared using Pepe and Mori test for equality of CIF across groups. [17] Revision was defined as the exchange, addition or removal of one or more components as registered in the LROI. Implant revision rate was calculated at 1 and 5 years postoperatively.

Furthermore, CIFs for revision were made for each covariables separated for HA and THA. Covariables used were sex, age (< 80 years vs. ≥ 80 years) (80 years was chosen since mean age was 80 year, range 50-107 years), ASA classification (I/II vs. III/IV), smoking status (yes/no), normal weight (BMI 18.5-25) was compared to overweight (BMI 25-30) type of approach (posterolateral (53%) or not posterolateral (anterolateral (12%), straight lateral (33%) and anterior (2%)) and type of stem fixation (cemented versus uncemented). A hybrid THA was classified according to whether the stem was cemented or not, in order to be able to compare with HA. Finally, HA type of head (unipolair versus bipolair head) was added to the analysis.

The Cox model in a multivariable approach with more covariables produces hazard ratios (HR) with 95% confidence intervals (CI). The estimated coefficients of the variables were tested if they were constant with time and if time interactions were statistically significant. The variables were entered as time-varying covariables

in the model when the proportional hazards assumption was violated. Separate proportional hazard models with hazard ratios (HR) are presented for HA and THA.

Results

30,830 acute hip fractures treated with a HA or a THA were registered in the LROI database between 2007 and 2017. In 22,675 fractures a HA was performed and in 8155 a THA. 79% received a unipolar HA, 20% a bipolar HA and 1% a monoblock HA. (table 1)

Table 1: Baseline characteristics and surgical details of patients with a hip fracture treated with a total hip arthroplasty (THA) or a hemi arthroplasty (HA)

		HA N= 22,675	**THA N= 8155**	**missing**
Sex	Female	70% (15,938/22,644)	70% (5672/8141)	45
Age	Mean (SD)	83 (7.7) *	71 (9.2)	12
ASA	ASA I/II	40% (8855/22,001) *	74% (5710/7743)	1085
Smoking #	yes	8% (729/8764) *	17% (526/3170)	18,896
BMI #	Mean (SD)	24 (9.4) *	25 (7.3)	17,062
Surgical approach	Posterolateral	53% (11,860/22,462) *	60% (4790/8046)	322
Stem fixation	Uncemented	34% (7578/22,442) *	57% (4584/8036)	352
Type of HA	Unipolar	79% (17,123/21,685)		990

Smoking and BMI are registered to the LROI database since 2014 * P<0.001

Revision rate

1-year revision rate in HA was (CIF (95% CI)) 1.6% (1.4 - 1.8) and 5-year 2.5% (2.3 - 2.8). (Figure 1, table 2) 1-year revision rate in THA was 2.4% (2.0 - 2.7) and 5-year 4.3% (3.8 - 4.8). (Figure 1, table 2) Revision rate was higher in THA (p<0.001).

Figure 1: Cumulative Incidence Function (CIF) of revision estimates from competing risks data (1-survival) for patients treated with HA and THA (n=30,830)

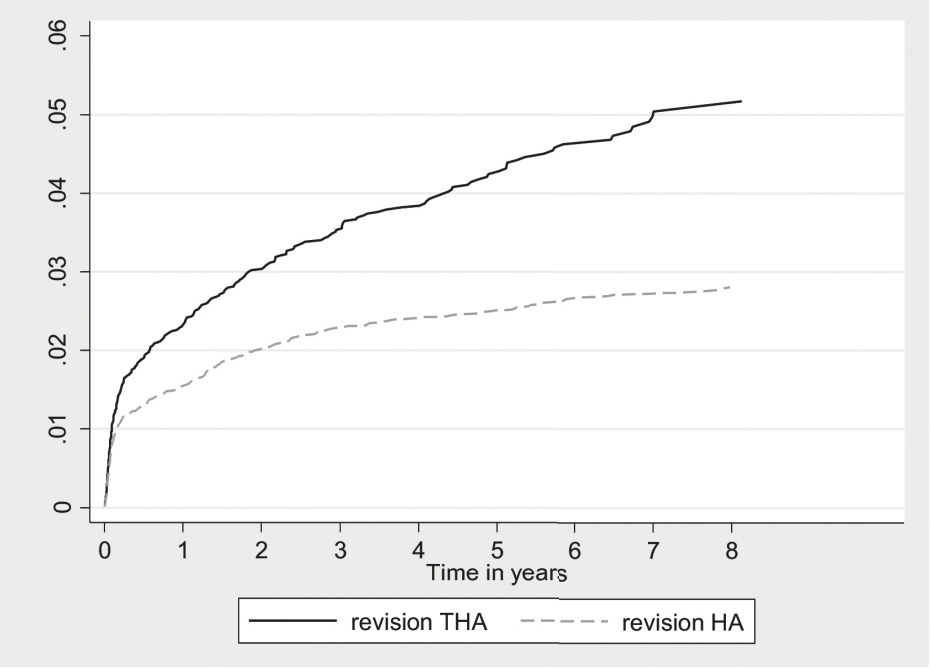


Table 2: Cumulative Incidence Function (CIF) estimates from competing risks data (1-survival) for patients treated with HA and THA

	Cumulative incidence of revision after 1 year	**Cumulative incidence of revision after 5 year**
HA	1.6% (1.4 % - 1.8%)	2.5% (2.3% - 2.8%)
THA	2.4% (2.0% - 2.7%)	4.3% (3.8% - 4.8%)

Reasons for revision

In 435 HA patients 1 reason for revision was given, in 66 patients multiple reasons were given (153 reasons in 66 patients). Dislocation, periprosthetic fracture and infection were the most common reasons for revision. In 228 THA patients 1 reason for revision was given, in 70 patients multiple reasons (156 reasons in 70 patients). Dislocation was the most common reason for revision (41%). (Table 3)

Table 3: reasons for revision after hemiarthroplasty (HA) or total hip arthroplasty (THA) for hip fractures.

	HA (n=501)	THA (n=298)
Single reason for revision, n	435	228
Dislocation, n (%)	128 (29%)	94 (41%)
Peri-prosthetic fracture, n (%)	58 (13%)	28 (12%)
Infection, n (%)	68 (16%)	26 (11%)
Loosening femoral component, n (%)	15 (3%)	25 (11%)
Loosening acetabular component or Cup/liner wear, n (%)	n/a	18 (8%)
Other reasons, n (%)	166 (38%)	37 (16%)
Multiple of above mentioned reasons, n	66	70

Risk factors for revision

Male sex, age below 80 years, ASA classification I/II, a posterolateral approach and uncemented fixation were risk factors for revision in HA in an univariable analysis risk (Figure 2, Table 4). A proportional hazard ratio model using all significant factors showed that male sex, age below 80 years, ASA I/II, a posterolateral approach and uncemented fixation are risk factors for revision (Table 5). Age and ASA classification were time varying covariables, meaning that the influence of these variables changes in time. For example, age is no risk factor for revision in the first year after the fracture, but becomes one in the years thereafter.

Male sex, age below 80 years, smoking, a posterolateral approach and uncemented stem fixation, were risk factors for revision in THA in an univariable analysis. ASA classification was not a clear risk factor (p=0.09) (Figure 2, Table 4). A proportional hazard ratio model showed that male sex, younger age, ASA III/ IV, a posterolateral approach and uncemented stem were associated with more revisions (Table 5). Age was a time varying covariable meaning that the hazard of age on revision changes in the time.

Table 4: Factors associated with revision in hip fracture patients after hemiarthroplasty (HA) and total hip arthroplasty (THA) in a univariable analysis with a hazard analysis

		HA		THA	
		HR	**95%CI**	**HR**	**95%CI**
Sex	Female (vs. male)	0.78 #	0.65-0.94	0.61 #	0.48-0.77
Age	> 80 (vs. < 80 years)	0.55 #	0.46-0.65	0.44 #	0.29-0.67
ASA	ASA III-IV (vs. I-II)	0.84	0.70-1.01	1.37*	1.06-1.76
Smoking	Yes (vs. no)	1.40	0.90-2.18	1.70*	1.02-2.83
Weight	Obesity (vs. normal BMI)	0.90	0.67-1.22	1.37	0.86-2.17
Approach	Non- posterolateral (vs. posterolateral)	0.67 #	0.56-0.80	0.68 *	0.54-0.88
Stem fixation	Cemented (vs. Uncemented)	0.61 #	0.51-0.73	0.73 *	0.57-0.93
Type of HA	Bipolar (vs. unipolar)	0.91	0.73-1.14		

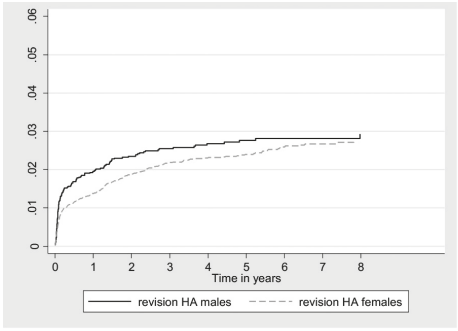
#= P<.001, *=P<0.05, HR= Hazard ratio

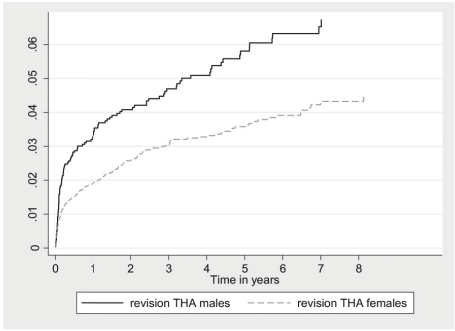
Table 5: Factors associated with revision in hip fracture treated with a total hip arthroplasty (THA) or a hemi arthroplasty (HA) in a multivariable approach with hazards model with time-varying covariables

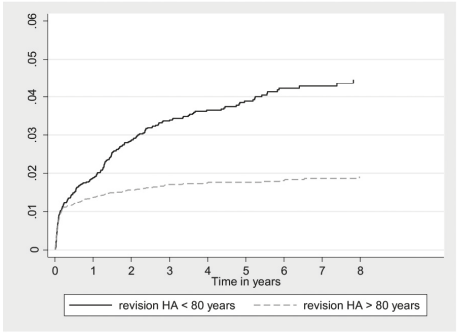
		HA		THA	
		HR	**95% CI**	**HR**	**95% CI**
Approach	Non posterolateral (vs. posterolateral)	0.67	0.55-0.81	0.70	0.55-0.90
Stem fixation [a]	Cemented (vs. Uncemented)	0.63	0.52-0.75	0.71	0.55-0.91
ASA [b]	ASA III-IV (vs. I-II)	0.72*	0.62-0.83	1.46	1.13-1.90
Age [c]	> 80 (vs. < 80 years)	0.59*	0.50-0.70	0.52*	0.55-0.91
Sex [c]	Female (vs. male)	0.80	0.66-0.97	0.65	0.51-0.83

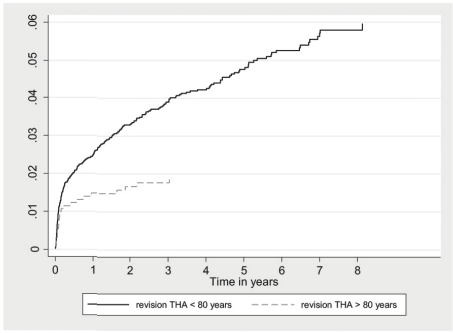
* Time-varying covariables, HR= Hazard Ratio [a] Variables with direct effect on outcome [b] Measured confounder with direct effect on choice of HA or THA [c] Measured confounders with effect on ASA
Confounder with direct effect on revision: HA / THA choice (not accounted for by stratification)

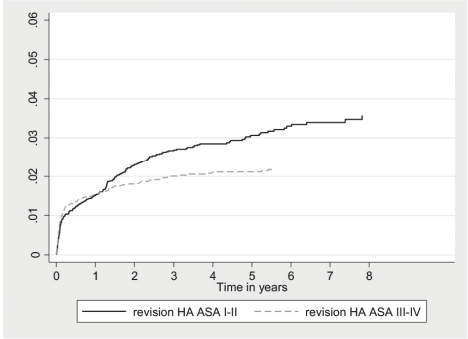
Figure 2; Cause- specific Hazard for revision for patients with a hip fracture treated with a Total Hip Arthroplasty (THA) or a Hemi Arthroplasty (HA)

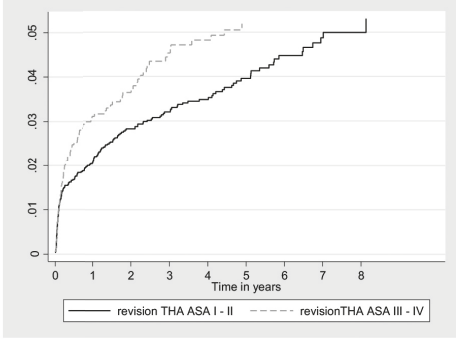


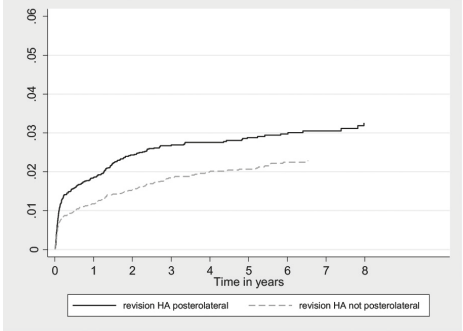


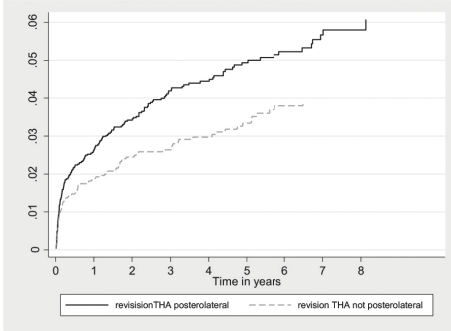


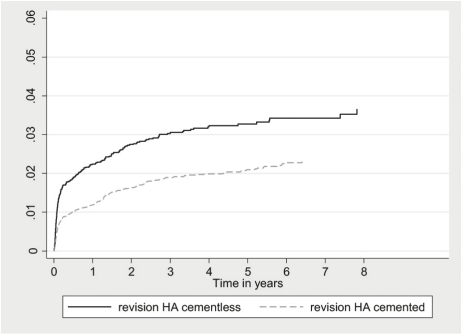


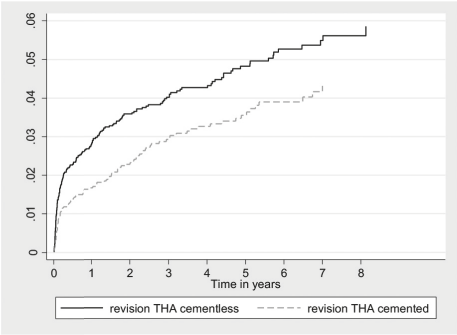


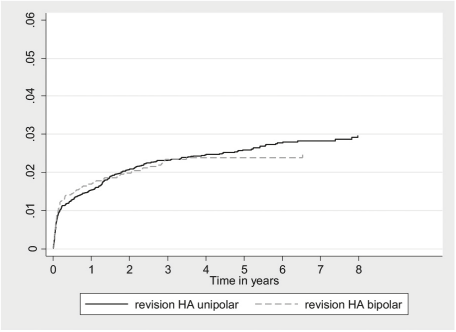












Specific reason for revision in factors associated with revision
In both THA and HA a fracture as a reason for revision was more common in an uncemented prosthesis (HA 28% vs 2%, THA 15% vs 6%). (Table 6)

In HA dislocation as a reason for revision was more common in younger patients (35% vs. 24%), ASA III/IV patients (35% vs. 24%) and a posterolateral approach (37% vs. 19%). A fracture was more common older HA patients (18% vs. 9%). Infection was more common amongst male patients (23% vs. 12%) and a cemented prosthesis (21% vs. 9%).

In THA dislocation as a reason for revision was more common in a cemented prosthesis (51% vs. 36%). A fracture as a reason for revision was more common in male sex (THA 18% vs. 8%).

Table 6: reason for revision in factors associated with revision in Hip fracture treated with a total hip arthroplasty (THA) or a hemi arthroplasty (HA).

		HA			THA		
		Dislocation	**Fracture**	**infection**	**Dislocation**	**Fracture**	**Infection**
All		128/435 (29%)	58/435 (13%)	68/435 (16%)	94/228 (41%)	28/228 (12%)	26/228 (11%)
Sex	Male	44/142 (31%)	16/142 (11%)	33/142 (23%)	35/94 (37%)	17/94 (18%)	11/94 (12%)
	Female	84/293 (29%)	42/293 (14%)	35/293 (12%)*	59/134 (44%)	11/134 (8%)*	15/134 (11%)
Age	< 80 years	53/222 (24%)	19/222 (9%)	27/222 (12%)	81/207 (39%)	26/207 (13%)	25/207 (12%)
	> 80 years	75/213 (35%)*	39/213 (18%)*	41/213 (19%)	13/21 (62%)	2/21 (10%)	1/21 (5%)
ASA	ASA I/II	54/209 (26%)	21/209 (10%)	29/209 (14%)	56/139 (40%)	17/139 (12%)	14/139 (10%)
	ASA III/IV	73/208 (35%)*	34/208 (16%)	38/208 (18%)	32/75 (43%)	10/75 (13%)	12/75 (16%)
Approach	Non-posterolateral	31/165 (19%)	25/165 (15%)	30/165 (18%)	24/74 (32%)	9/74 (12%)	11/74 (15%)
	Posterolateral	96/262 (37%)*	32/292 (12%)	38/262 (15%)	70/152 (46%)	18/152 (12%)	15/152 (10%)
Fixation	Cemented	81/243 (33%)	5/243 (2%)	52/243 (21%)	42/82 (51%)	5/82 (6%)	11/82 (13%)
	Uncemented	46/183 (25%)	52/183 (28%)*	16/183 (9%)*	51/142 (36%)*	22/142 (15%)*	14/142 (10%)

* p≤0.05

Discussion

Revision rate of THA was higher compared to the revision rate of HA. The 5-year revision rate of a HA was 2.5% and 4.3% in THA, which is in contrast to the results from randomized trials, that showed no difference between HA and THA. [18, 19] However, patients included in these randomized trials were less frail than the average hip fracture patients. The HA group in our registry study contained patients with more frailty (higher age, higher ASA classification) than the THA group: therefore, the threshold for a surgeon to decide to revise was probably higher in the HA group.

In our study, dislocation was the most common reason for revision in both HA (29%) and THA (41%). Acetabular erosion (prevalence is 2 to 41 %) is a theoretical

indication to perform a revision in a painful HA. [20] In the LROI, acetabular erosion as reason for revision cannot be registered. Patients who were revised for acetabular erosion were classified in the 'other' category (38%). How many patients in this category had acetabular erosion is unclear.

Male sex and age below 80 years were risk factors for revision surgery in THA and HA. This in accordance with data from the Norwegian and British register. [21, 22] Younger patients are likely to be more demanding regarding hip function after surgery, thus even revision for moderate postoperative complaints are more likely. Males have an higher occurrence of periprosthetic fractures, what may lead to a higher revision rate (Table 6). [23]

In HA, ASA classification I/II was a risk factor for revision, however in THA ASA classification III/IV was a risk factor for revision. This contradiction is probably explained by the selection bias of THA and HA. We believe THA patients with an ASA classification III/IV are less frail than HA with ASA classification III/IV, while a surgeon will choose a HA in the frailest patients (i.e. shorter surgical time and less blood loss [24]). These frail HA patients (ASA classification III/IV) are unlikely to undergo revision due to higher risks but also to lower demand on functionality of these patients. In THA these ASA classification III/IV patients have a higher risk of revision compared to ASA classification I/II. Comorbidities like diabetes mellitus might cause this higher change of infection. [25] A British and Norwegian register study has shown the same tendency of higher revision in higher ASA patient in THA for hip fracture. [22, 25]

A posterolateral approach was a risk factor for revision in both HA and THA. 2 Large register studies showed that the posterolateral approach led to more dislocations. [6, 21] However, Patient Reported Outcome Measurements (PROMs) used in the registry study in Norway showed that the posterior approach gave less pain, less walking problems and better QoL than the lateral approach. [26] Using a dual mobility cup may reduce dislocation risk when using a posterolateral approach. [27–29]

Uncemented stems were a risk factor for revision in both HA and THA. Peri-prosthetic fractures are more common in uncemented prosthesis (both HA and THA), probably as a result of trying to create a press fit situation in the weaker (osteoporotic) bone. [30] This increased risk of periprosthetic fracture in

uncemented prosthesis must be weighed against the potential complications of cementing such as Bone Cement Implantation Syndrome (BCIS). [31]

Bipolar prosthesis are developed to reduce the risk of erosion of the acetabulum. We did not find any difference in revision hazards between unipolar and bipolar heads. 79% of the Dutch hip fracture patients treated with HA receive an unipolar head. Costs for bipolar heads in the Netherlands are about double the costs of unipolar heads. The Swedish register showed more reoperations with bipolar heads [6] and the Australian register found less reoperation rates with bipolar head [5]. Reasons for these conflicting data may be the difference in hemiarthroplasty populations in Australia, Sweden and the Netherlands. The NICE guideline [32] for hip fractures advises against use of monoblock prostheses. In our register only 164 (0,8%) of all HA were monoblock prosthesis. Therefore no analysis on these monoblock prosthesis was performed.

This is the first nationwide Dutch study on HA and THA in acute hip fractures using data from the Dutch Arthroplasty Register (LROI). Previously the Scandinavian, British, and Australian registers have published their results. [4–6, 22] The added value of these Dutch results is important, since each country has its own specific health care organization. As for the Netherlands, a quality mark for hip fractures was that surgery has to be performed within 24 hours of admittance which may cause difference in outcome between registers. Furthermore, this study includes both HA and THA data for acute hip fractures. Observational data studies for THA in hip fractures are sparse, thus knowledge on this subject has to be extended, since the proportion of hip fracture patients treated with THA is increasing. The proportion hazards model clearly assigns risk factors for revision, which is of clinical importance and may guide treatment of these often frail patients in order to minimize the perioperative risks.

Limitation of the study is the incomplete registration of HA for acute hip fractures (but still 88% completeness). Follow up of hip fracture patients is limited because of the high mortality rate (1-year mortality is around 20%). There is a limited number of patient characteristics registered in our national registry. Alcohol use for instance, was not registered although it influences revision rate. [33, 34] Because of this limited number of patient characteristics, there is potential for residual confounding. Furthermore, only revision operations in which components are replaced are registered to the database. Reoperations without component

(re-)placement (like debridement of the wound and the prosthesis without liner exchange in case of acute infection) are not registered to the LROI database.

In summary revision rates in both HA and THA after an acute hip fracture are considerable. Avoidance of uncemented stem and posterolateral approach may reduce the revision rate.

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CHAPTER 3

MORE COMPLICATIONS IN UNCEMENTED COMPARED TO CEMENTED HEMIARTHROPLASTY FOR DISPLACED FEMORAL NECK FRACTURES. A RANDOMIZED CONTROLLED TRIAL OF 201 PATIENTS, WITH ONE YEAR FOLLOW-UP.

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BMC Musculoskeletal Disorders (2017) 18:169

Abstract

Introduction

It is unclear whether cemented or uncemented hemiarthroplasty is the best treatment option in elderly patients with displaced femoral neck fractures. Previous randomized trials comparing cemented and uncemented hemiarthroplasty have conflicting results. We conducted a randomized controlled trial to compare cemented and uncemented hemiarthroplasty.

Methods

This multicenter parallel-randomized controlled trial included patients of 70 years and older with a displaced femoral neck fracture (Garden type III or IV). Inclusion was between August 2008 and June 2012. Patients were randomized between a cemented hemiarthroplasty, type Müller Straight Stem or an uncemented hemiarthroplasty, type DB-10. Primary outcomes were complications, operation time, functional outcome (measured by Timed-Up-and-Go (TUG) and Groningen Activity Restriction Scale (GARS)) and mid-thigh pain. Health Related Quality of Life (HRQoL, expressed with the SF-12) was measured as an secondary outcome. Follow up was one year.

Results

In total 201 patients were included in the study (91 uncemented, 110 cemented hemiarthroplasties) The uncemented group showed more major local complications (intra- and postoperative fractures and dislocations) odds ratio (95% confidence interval) 3.36 (1.40 to 8.11). There was no difference in mean operation time (57.3 vs 55.4 minutes). There were no differences in functional outcomes (TUG 12.8 (9.4) vs. 13.9 (9.0), GARS 43.2 (19.7) vs. 39.2 (16.5)) and mid-thigh pain (18.6% vs 21.6%). Physical component SF-12 HRQoLwas lower in the uncemented group (30.3 vs. 35.3 $p<0.05$ after six weeks, 33.8 vs 38.5 $p<0.05$ after 12 weeks).

Conclusion

A cemented hemiarthroplasty in elderly patients with a displaced femoral neck fracture results in less complications compared to an uncemented hemiarthroplasty.

Introduction

Hip fractures are a rising problem in our aging society. An increase in the incidence of hip fractures in Europe from 615.000 in 2010 to 815.000 in 2025 (+32%) due to demographic changes is expected. [1] Elderly patients with a dislocated femoral neck can be treated effectively with hemiarthroplasty. [2] However, there is a persistent controversy regarding the use of cement. [3] In cemented hemiarthroplasties, polymethylmethacrylate bone cement is used during surgery to create a solid bone-implant interface. A potential advantage of cement is less post-operative mid-thigh pain, as the hemiarthroplasty is more firmly fixed within the femur. [4] A potential negative effect of using cement is the Bone Cement Implantation Syndrome (BCIS), characterized by hypoxia and/or hypotension in combination with an unexpected loss of consciousness which occasionally occurs following cement insertion. [5] This complication may be fatal.Uncemented hemiarthroplasties are placed press-fit in the femur. In the weeks after the surgery the bond between femur and the stem is dependent on osseous integration.[6] However, bone quality is generally poor in elderly hip fracture patients, which may lead to periprosthetic fractures during press-fit placement or inadequate bony in-growth post-operatively. [7] Both NICE and AAOS guidelines advise to use cemented implants. [2] [8] However, despite these guidelines, database studies show that 22 % to 34 % of the hemiarthroplasties are used without cement. [9] [10]

The Cochrane review of 2011 included six trials comparing cemented and uncemented hemiarthroplasty and demonstrated a reduction of the amount of postoperative pain, an improvement in postoperative function and less implant-related complications when cement was used, but a longer operation time. There was no difference in adverse events or mortality. [3] After this review three more randomized trials were published. One found no difference in functional outcome, complications and mortality. [11] Another found more complications (subsidence, intraoperative fracture and postoperative fracture) in the uncemented group, with no differences in pain or mortality. [12] The third trial found better functional outcomes and less intraoperative fractures in the cemented group. [13] Thus the controversy whether to use a cemented or uncemented hemi arthroplasty in the older patients with a displaced femoral neck fracture persists.

Therefore, we compared uncemented and cemented hemiarthroplasties in a parallel randomized controlled trial. We hypothesized that an uncemented hemiarthroplasty for a displaced femoral neck fracture in elderly patients would have at least comparable radiological and functional outcomes and complication

rate as a cemented hemiarthroplasty and that non-cementing of hemiarthroplasty would result in a shorter operation time. [14]

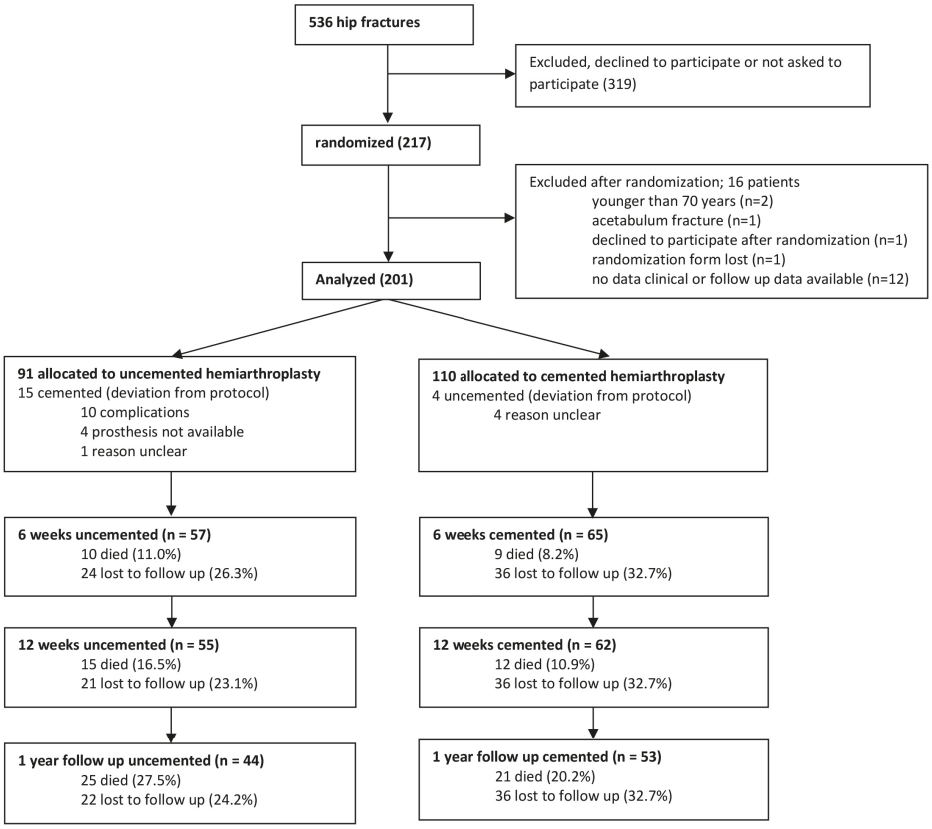
Methods

This multicenter parallel randomized controlled trial included patients with a displaced femoral neck fracture. The study was approved by the Regional Ethics Committee (NL19200.098.07, METC07-118). The trial was registered in the Netherlands Trial Registry NTR 1508 (http:/ /www.trialregister.nl). The protocol was published before start of the study. [14]

All patients were admitted to one of the participating hospitals (Reinier de Graaf hospital, Delft; Rijnstate hospital, Arnhem and Canisius Wilhelmina hospital, Nijmegen), large district hospitals in the Netherlands. Inclusion was between August 2008 and June 2012. Included were patients aged 70 years or older, with a displaced femoral neck fracture (Garden type III or IV) suitable for hemiarthroplasty. Excluded were patients with a pathological fracture, a fracture older than seven days or ASA-IV or V classification. Orthopedic residents, trained for this study, performed inclusion. All patients gave informed consent. In case of (mental) incompetence of the patient, his or her legal representative was consulted to obtain informed consent. Patients were randomized following a simple randomization procedure in the operation theatre by the orthopedic surgeon through opaque sealed envelopes. These were prepared by A.J.V. and kept at the operation theatre of each of the three hospitals. 200 opaque sealed envelopes were prepared. However, 16 patients could not be included in our trial due to variable reasons (figure 1), which forced us to prepare another 16 envelopes.

The patients were blinded for the type hemiarthroplasty they received, although we acknowledge the possibility that they might be able to tell after seeing their radiographs during the outpatient clinic visits. Surgeons and outcome assessors were aware of the allocated arm.

Figure 1; flowchart of the recruitment and flow of patients with femoral neck fractures during the study



Patients received a cemented hemiarthroplasty, type Müller Straight Stem (Zimmer - Biomet, 1800 West Center St. Warsaw, Indiana, USA) or an uncemented hemiarthroplasty, type DB-10 (Zimmer- Biomet, 1800 West Center St. Warsaw, Indiana, USA). The cemented hemiarthroplasty, the Muller straight stem has a small proximal collar and two longitudinal grooves to enable good cement adhesion. The non-cemented DB-10 is a straight collared stem with metaphyseal anchoring and on the surface full hydroxyapatite coating on macro-structured titanium and grooves. If complications occurred during the procedure, the surgeon could change the procedure to ensure best medical practice. Operating technique was according to the manufacturer instruction. In the participating hospitals there was experience with both cemented and uncemented hip arthroplasty. Either an orthopedic surgeon or registrar performed the operation. Cementing technique involved

vacuum mixing, cement plug, saline pulsed lavage and retrograde introduction of cement with a cement gun. The approach was up to the surgeon's preference, as Parker's Cochrane analysis has shown that insufficient evidence is available for superiority of either approach [3].Each patient received physiotherapy therapy, analgesia and trombo-embolic prophylaxis according to the protocol of the hospital in which they were treated.

Preoperatively, social demographic data (age, sex, place of residence), ASA-(American Society of Anesthesiologists) classification [15], Body Mass Index (BMI), Minimal Mental State Examination (MMSE) [16] were obtained. Patients were asked to score their pre-fracture mobility and Health Related Quality of Life (HRQoL) using the New Mobility Score (NMS) [17], Groningen Activity Restriction Scale (GARS) [18] and the SF-12 [19]. Patients were asked if they mobilized with an aid indoors and outdoors with or without aid and whether they received homecare. The baseline hemoglobin level was measured. The surgical approach, the type of surgeon (consultant or registrar) and kind of anesthesia were registered.

Outcomes measured during operation were operation time (defined as skin-to-skin surgical time, measured in minutes) and blood loss (in centiliter, estimated by the surgeon). Length of stay, decrease in hemoglobin level and transfusion rate were measured postoperatively.

All patients were invited for follow up at six, 12 and 52 weeks postoperatively. When the patient was not able to visit the outpatient clinic, the questionnaires were mailed to the patient or its relatives. During follow-up functional outcome was measured using Timed-Up and- Go (TUG) score [20], GARS [18] and NMS [17]. HRQoL, expressed in the SF-12 [19], was measured. The SF-12 was divided in a Physical Component summary Score (PCS) and a Mental Component summary Score (MCS). Mid-thigh pain (defined as pain explicitly in the front and mid part of the femur) pain and place of residence were registered. Complications during surgery, hospital stay and the year thereafter were recorded. The complications were defined and ranked in the modified Elixhauser mode, as described by Parvizi. [21] Mortality was scored meticulously by repeated consultation of the population registers of the counties in the region of the hospital as well as the hospital's patient registration systems for the full length of follow-up.

A radiograph was obtained on the first postoperative day and after six weeks, 12 weeks and one year. Adequate positioning of the stem was defined as within

10 degrees varus or valgus position with respect to the femoral axis. Fissures, fractures, subsidence and loosening were noted.

Analysis
Primary outcomes were complications, operation time, functional outcome and post-operative mid-thigh pain. A Bonferroni correction was applied for the eight primary outcome measures (4 types of complications, operation time, GARS, TUG and mid-thigh pain at one year) making $p < 0.006$ significant. Secondary outcomes were return to place of residence as percentage of pre-fracture situation, HRQoL and adequate radiological positioning of the hemiarthroplasty. [14]

Determination of sample size
The complete power calculation is published in our protocol [14] We expected (based on the literature in 2008) that midthigh pain in uncemented prosthesis would be 30% and in cemented prosthesis 7.5%.

$$\pi 1 = 30\%, \pi\ 2 = 7.5\%, \pi = (30\%+7.5\%)/2 = 18.75\%$$
$$n1 = n2 \geq 21^* (0{,}1875^*(1\text{-}0{,}1875))/(0{,}225)2 = 63.2$$

While we expected 25% 1-year mortality and 10% lost-to follow-up we raised this number by 35%. Thus a total of 86 patients a group were needed. The calculations for the other three primary outcome measures (duration of surgery, functional outcome and complications) produced lower patients numbers. [14] From a practical point of view we choose a total of 100 patient per group. All analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA). The differences in outcome measures were analyzed using an independent sample student T-test (for continuous data) and Chi-Square Test (for categorical data), setting the level of significance at $p < 0.05$ for secondary outcomes. All outcomes analyses were done twice: both for as treated analysis and for intention to treat. The numbers given in the results section represent the intention to treat analysis. We will report explicitly if differences exist between as treated analysis and intention to treat analysis.

Results

In total 201 patients were analyzed. (Figure 1) 91 Were randomized to an uncemented, 110 to a cemented hemiarthroplasty. In 15 of the 91 (16%) patients randomized to an uncemented hemiarthroplasty a cemented hemiarthroplasty was used instead. In ten patients this was due to intraoperative complications (i.e fracture of the femur). In four patients the necessary instruments or prosthesis

were not present and in one patient the reason was unknown. Four of the 110 (4%) patients randomized to a cemented hemiarthroplasty received an uncemented hemiarthroplasty. In none of these cases the reason for this breach of the protocol was clear. Table 1 shows baseline characteristics of both groups.

Table 1: baseline characteristics

	Uncemented (91)	**Cemented (110)**
Age (mean (SD))	84.0 in 91 (6.7)	83.0 in 110 (6.2)
Sex female (number, %)	61 out of 91 (67%)	82 out of 110 (75%)
ASA classification (number, %)		
I	7 out of 91 (8%)	6 out of 110 (6%)
II	51 out of 91 (56%)	71 out of 110 (65%)
III	33 out of 91 (37%)	33 out of 110 (30%)
BMI (mean (SD))	24.3 in 60 (3.5)	24.1 in 73 (3.4)
MMSE < 24 (number, %)	15 out of 44 (34%)	23 out of 56 (41%)
Mobile without aid indoors (number, %)	32 out of 73 (44%)	41 out of 81 (51%)
Mobile without aid outdoors (number, %)	21 out of 73 (29%)	32 out of 81 (40%)
NMS (mean (SD))	5.2 in 71 (2.7)	5.5 in 77 (3.0)
GARS (mean (SD))	41.1 in 71 (16.8)	41.7 in 78 (18.6)
SF-12, Physical Component (mean (SD))	37.1 in 65 (11.2)	37.9 in 65 (12.3)
SF-12, Mental Component (mean (SD))	46.8 in 65 (10.9)	48.3 in 65 (12.1)
Living at home (number, %)	52 out of 73 (71%)	58 out of 84 (69%)
No domestic or homecare (number, %)	37 out of 64 (58%)	39 out of 75 (52%)
Hemoglobin level (g/dL) (mean (SD))	12.8 in 91 (1.5)	12.7 in 110 (1.8)
Surgical approach (number, %)		
Straight lateral	41 out of 90 (46%)	49 out of 110 (45%)
Postero lateral	45 out of 90 (50%)	61 out of 110 (55%)
Anterior	4 out of 90 (5%)	
Consultant (vs. registrar) (number, %)	24 out of 91 (26%)	43 out of 110 (39%)
Spinal anesthesia (vs. general) (number, %)	68 out of 90 (76%)	80 out of 107 (75%)

Primary outcomes;

Complications

The one-year complication rate per category as categorized by Parvizi is shown in table 2. [21] Major local complications were more frequent in the uncemented hemiarthroplasty group; (odds ratio; 95% CI) (3.36; 1.40 to 8.11). In the uncemented group there were 14 periprosthetic fractures. 12 were noticed perioperative, in ten of these patients the procedure was converted to a cemented procedure, in two patients a cerclage wire was used. In two patients of the uncemented group and 3 of the cemented group a fracture was noted postoperative, these patients were

treated with protected weight baring. Analysis according the as treated analysis approach (instead of intention to treat) showed no differences between cemented and uncemented hemiarthroplasty regarding major local complications. Minor local complications (0.73; 0.33 to 1.59), major systemic (1.31; 0.71 to 2.41) and minor systemic complications (0.96; 0.47 to 1.93) were comparable between groups. The one-year mortality rate was higher in the uncemented group (25 (27.4%)) compared to the cemented group (21 (19.0 %)) but did not reach significance (p= 0.18). One major systemic complication was a patient who died just after injecting the cement into the femoral canal, potentially caused by BCIS, however autopsy was not performed.

Operation time

The mean (95% CI) operation time was comparable between uncemented and cemented hemiarthroplasty: 57.3 minutes (52.8 – 61.9) and 55.4 minutes (52.0 – 58.9) respectively.

Functional outcome

At no point of follow-up a difference was found in functional outcome, expressed in the TUG and GARS score (Table 3). The pre-defined clinically relevant worsening from 30 to 42 of the TUG was not met in a single patient in one of the groups. TUG was poorly registered (53% at six weeks, 51% at 12 weeks, 48% at one year, corrected for mortality).The NMS was at all moments of follow-up comparable (Table 3).

Post-operative mid-thigh pain

There was no difference in post-operative mid-thigh pain between both groups at any time during follow up. It was present in 43 patients (36 %) after six weeks, which decreased to 31% after 12 weeks and 20% after one year. (Table 3)

Table 2; one-year complication rate per category as categorized by Parvizi.

		Uncemented (91)	**Cemented (110)**	**P**
Major systemic	Death	25	21	(0.18)
	Tachyarrhythmia	1	4	
	Myocardial infarction	4	2	
	Pulmonary embolus	1	6	
	Acute renal failure	3	2	
	Stroke and/ or TIA	3	3	
	Bowel obstruction	0	1	
	Total number of patients with >/=1 major systemic complication*	29 out of 91 (31.9%)	29 out of 110 (26.4%)	0.41
Minor systemic	Anemia	30	39	
	Urinary tract infection	14	22	
	Mental status change	23	21	
	Gastric hypomotility	0	2	
	Deep venous thrombosis	0	1	
	Pneumonia	14	12	
	Social complication	2	9	
	Others	2	2	
	Total number of patients with >/=1 minor systemic*	73 out of 91 (80.2%)	89 out of 110 (80.9%)	0.92
Major local	Peripheral nerve injury	0	1	
	Infection leading to revision	0	1	
	Periprosthetic fracture	14	3	
	intraoperatively	*12*	*0*	
	postoperatively	*2*	*3*	
	Dislocation	5	3	
	Total number of patients with >/= 1 major local complication*	19 out of 91 (20.9%)	8 out of 110 (7.3%)	0.005
Minor local	Hematoma	1	6	
	Persistent wound drainage	3	4	
	Superficial wound infection	3	6	
	Skin blisters	1	1	
	Other	6	2	
	Total number of patients with >/= 1 minor local complication*	12 out of 91 (13.2%)	19 out of 110 (10.9%)	0.42

*The number of patients with a complication in a category is not equal to the sum of complications in a category, while some patients had more than 1 complication.

Table 3 functional outcome measures at six, 12 weeks and one year and radiological outcome post-operative and any time during follow up

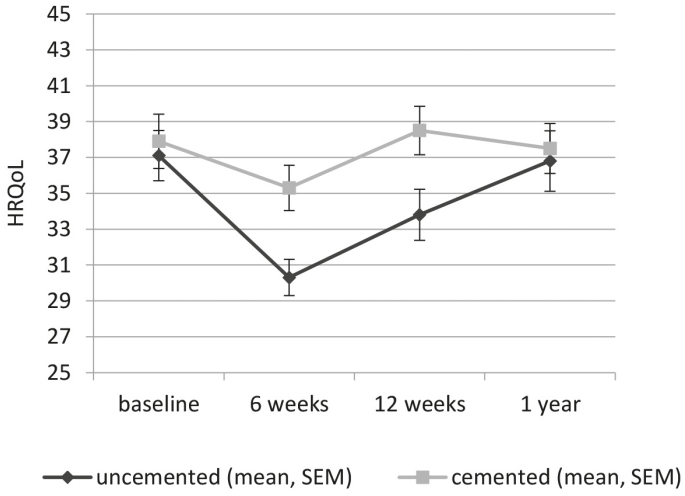
		Uncemented			Cemented			
		Mean (SD)	**97.5% CI**	**N**	**Mean (SD)**	**97.5% CI**	**N**	**P**
Timed Up and Go	6 weeks	18.7 (13.8)	13.9-23.5	45	18.7 (12.9)	14.6-22.9	51	0.99
	12 weeks	16.2 (12.4)	11.5-20.9	38	15.5 (8.5)	12.7-18.2	50	0.74
	one year	12.8 (9.4)	8.9-16.7	33	13.9 (9.0)	10.1-16.7	41	0.79
GARS (iADL)	6 weeks	53.1 (14.9)	48.5-57.8	54	50.0 (15.3)	45.7-54.4	65	0.27
	12 weeks	45.7 (17.0)	40.3-51.2	52	45.3 (16.6)	40.4-50.1	62	0.88
	one year	43.2 (19.7)	36.2-50.2	43	39.2 (16.5)	34.0-44.4	53	0.28
NMS	6 weeks	3.7 (2.5)	2.9-4.4	53	3.5 (2.4)	2.8-4.1	64	0.65
	12 weeks	4.5 (2.8)	3.6-5.4	51	4.8 (3.1)	3.8-5.7	59	0.68
	one year	4.7 (3.2)	3.6-5.8	44	5.7 (2.9)	4.8-6.7	50	0.12
SF-12 Physical component	6 weeks	30.3 (6.9)*	27.9-32.6*	47	35.3 (9.3)*	32.4-38.2*	54	0.003
	12 weeks	33.8 (9.8)*	30.6-37.1*	48	38.5 (9.9)*	35.4-41.6*	54	0.018
	one year	36.8 (10.7)	32.9-40.8	40	37.5 (9.4)	34.3-40.7	50	0.76
SF-12 Mental Component	6 weeks	45.0 (13.0)	40.7-49.5	47	47.4 (11.0)	44.0-50.8	54	0.33
	12 weeks	47.7 (11.2)	43.9-51.4	48	49.5 (11.0)	46.0-52.9	54	0.41
	one year	49.3 (11.2)	45.2-53.4	40	51.4 (10.1)	47.9-54.9	50	0.36
		Number (%)			Number (%)			
Mid-thigh pain	6 weeks	23 out of 55 (42%)			20 out of 63 (32%)			0.26
	12 weeks	19 out of 55 (35%)			17 out of 61 (27%)			0.83
	one year	8 out of 43 (19%)			11 out of 51 (22%)			0.72
X ray varus or valgus deviation	Post operative	8 out of 89 (9%)			7 out of 107 (7%)			0.76

*<0.05

Secondary outcomes;

There was no difference in the number of patients who returned to their baseline place of residence after one year (28 patients (72%) vs. 37 patients (80%) p=0.88). The SF-12 MCS did not differ between the cemented and the uncemented group. (Table 3) However, the SF-12 PCS was lower at six and 12 weeks postoperatively in the uncemented hemiarthroplasty group. This difference resolved after one year. (Table 3 and Figure 2) Analyzing the results according the as treated analysis showed a lower PCS for uncemented hemiarthroplasty at six weeks (30.3 vs. 34.8 p=0.01), and a difference at 12 weeks (34.0 vs. 37.9) which nearly did reach significance (p=0.056). There was no difference at one year after surgery (36.6 vs.37.6 p=0.65)

Figure 2; Health Related Quality of Life, Physical Component Score



Radiographs were taken direct post-operative and after 6 and 12 weeks and one year. Five patients deceased before the post-operative radiograph was obtained. Eight varus or valgus deviations in the uncemented group and seven in the cemented group (p=0.76) were found on the post-operative radiograph. Loosening or subsidence was observed in 13 (20%) of the uncemented and five (6%) of the cemented hemiarthroplasties (p= 0.007) any time during follow up. Four (2%) revision operations were performed: three due to loosening (all in the uncemented group) and one for infection (in the cemented group). (p=0.162)

There were no differences in length of stay between both groups (mean 11 (SD 7.7) days uncemented vs. 11 days (SD 8.3) cemented p=0.83), loss in hemoglobin level (g/dl) after surgery (uncemented mean 2.2 (SD 1.4) vs. cemented mean 2.0 (SD 1.5) p=0.31) and transfusion rate (uncemented 17 (24%) vs. cemented 22 (26%) p=0.74). Surgeon estimated blood loss was larger in the uncemented group (mean 288 mL (sd 213) vs. mean 220 mL (sd 143) p=0.03). (additional table 1)

Additional Table; perioperative details of uncemented and cemented hemiartroplasty

	uncemented		cemented		
	Mean (SD)	N	Mean (SD)	N	p
Length of stay (days)	10.51 (7.6)	91	10.76 (8.33)	110	0.83
Loss in hemoglobin level (g/dL)	2.20 (1.35)	91	1.98 (1.54)	109	0.31
Estimated blood los (mL)	288 (213)	71	220 (143)	73	0.027
	Number (%)		Number (%)		
Transfusion rate	17 out of 72 (23.6%)		22 out of 85 (25.9%)		0.74

Discussion

The most important finding of our study was that major local complications were more frequent (odds ratio; 95% CI) (3.36; 1.40 to 8.11) in the uncemented hemiarthroplasty group compared to the cemented group. In elderly patients with a displaced femoral neck fracture hemiarthroplasty is a widely accepted treatment of choice. [2] Previous randomized trials comparing cemented and uncemented hemiarthroplasty give conflicting results on this. [4, 11–13, 22]

A periprosthetic fracture was the most common major local complication in the uncemented group (15%). Previous papers comparing fracture rate are heterogenic. Some studies found a higher fracture rate in the uncemented group, ranging from 5.5% to 12% [3, 12, 13, 23] whereas others demonstrated no difference in fracture rate. [4, 11, 22] The fracture rate in the current study is higher than previous papers demonstrate. This can be due to the design of the DB-10 stem (proximal fitting) compared to the stems used in the other papers. Furthermore, teaching of registrars might have attributed to this as well: the level of experience of the operation surgeon is not always mentioned, but for example in the studies of Inngul, DeAngelis and Parker the operations were always performed by consultant orthopaedic surgeons. [4, 11, 13] However this high complication rate might better reflect the everyday practice with registrars often performing this type of operations

One-year mortality rate was higher in the uncemented group (25 (27.4%) compared to the cemented group 21 (19.0 %) but did not reach significance (p= 0.16). This is in contrast to other randomized controlled trials. [4] The register studies show higher mortality in the first operative days in cemented hemi arthroplasty [24–26]. However the Australian and British register shows lower mortality in cemented hemiarthroplasty the year thereafter.[27] [10] Power analysis in our study was not performed on finding differences in mortality. In our trial one patient died

intraoperatively, probably due to Bone Cement Implantation Syndrome (BCIS). BCIS is a major side effect of cement implantation, it has no agreed definition but is characterized by a number of clinical features with amongst others hypoxia, hypotension, cardiac arrhythmias, increased pulmonary vascular resistance and cardio-respiratory collapse. [5] Guidelines to minimize the risk for BCIS by both surgeon and anesthetist are recently published. [28]

In contrast to our hypothesis and literature, we did not find a difference in operation time between groups. [3] [22] Intraoperative complications in the uncemented group might have affected this, however equality in the mean operation time persisted when we analyzed our data in an As Treated analysis. Teaching residents might have affected the operation time in such way that the difference disappeared.

Functional outcome (GARS score and TUG test) was not different between both groups. However TUG was measured only in 53% of all patients at 6 weeks, 51% at 12 weeks and 48% at one year. Probably TUG is not a very useful outcome measure in this frail population as mobility was too poor to measure well. Mobility expressed as the NMS was comparable between the two groups. In literature different outcome measures for functional outcome have been used (Oxford or Harris Hip Score [12, 13, 22] Older Americans Resources and Services Instrument [11] Barthel Index [22]). A meta-analysis pooled results of five trials (491 patients) and found that patients with an cemented hemiarthroplasty had a better hip function after one year. [7]

Mid-thigh pain is known to be more prevalent in uncemented prostheses, however the reported incidence differs tremendously. [4, 7, 29] In our study presence of mid-thigh pain was comparable between groups. Several factors can be of influence on post-operative mid-thigh pain such as sizing, design and stiffness of a prosthesis. [29]

Radiological follow up showed loosening or subsidence in 13 uncemented hemiarthroplasty, which led to a revision in three cases. Subsidence in uncemented (hemi) arthroplasty is a common finding. [12] In The Norwegian Hip Fracture Register patients treated with an uncemented hemiartroplasty had a 2.1 times increased risk of revision compared with patients treated cemented prostheses. This increased risk of re-operation was due to peri-prosthetic fracture HRR 17 and aseptic loosening HHR 17. [30] A combined analysis of the Norwegian and

Swedish registers (33.205 hip fractures in patients older than 60 years treated with hemiarthroplasty) also found more reoperations in uncemented stems (HR 2.2) [9]

PCS of HRQoL was lower in patients treated with an uncemented hemiarthroplasty at six weeks and three months after surgery. PCS HRQoL is known to decrease in the first three months and recover thereafter. [31] The larger complication rate might have led to this lower PCS HRQoL, although we would have expected to find a difference in functional and mobility scores as well. One previous trial found higher HRQoL (expressed in EQ5D) in the cemented group [13] at 4 and twelve months, another trial did not. [22] The latter did not find a difference in complications either. [22] HRQoL was an secondary outcome in this trial, thus no power calculations were made and dropout at follow-up was quite high: therefore the difference we found might be due to coincidence and has to be verified in further trials.

The large number of patients, the randomized design and outcome measures on both functional and radiological outcomes make the current study worthwhile. Furthermore, we did not exclude patients with cognitive disorders. The latter makes our study generalizable to all elderly hip fracture patients treated with hemiarthroplasty.

However, our study does have limitations. First, many (293) patients (or their caretakers) declined to participate in our study or were not asked to participate, thus selection bias might be present. Second, poor registration has led to incompleteness of some of the baseline data. This led to the exclusion of 12 patients after randomization because of missing baseline data, 5 patients were excluded after randomisation due to other reasons (figure 1). Deviation from the protocol occurred in 19 patients (9% of analyzed cases). Therefore both as treated analysis and intention to treat were performed. More deviations from protocol were present in the uncemented group (15 vs. 4) which might have caused a bias. Furthermore, we had a substantial percentage (24%) of patients who were lost to follow-up. This might be due to the inclusion of patients with cognitive disorders (38% had an MMSE less than 24) and high age of the participators, resulting in their caretakers to refrain from extra stress by those patients by filling in follow-up forms. This trial adds value to the discussion whether to use a cemented or an uncemented hemiartroplasty in femoral neck fractures. Conflicting evidence on this matter is published the last few years. [4, 11–13, 22] Trial design, prosthesis design, inclusion criteria and whether the trail was performed in a teaching hospital or not might all have been of influence of these published results.

Elderly patients with a displaced femoral neck fracture treated with an uncemented hemiarthroplasty had more periprosthetic fractures, loosening, reoperations and lower quality of life compared to patients with a cemented stem. Operation time, functional outcome and mid-thigh pain were comparable between groups. Based on these findings, and earlier work [3, 12, 13] we conclude that in elderly patients with a displaced femoral neck fracture a cemented hemiarthroplasty is favorable compared to an uncemented stem.

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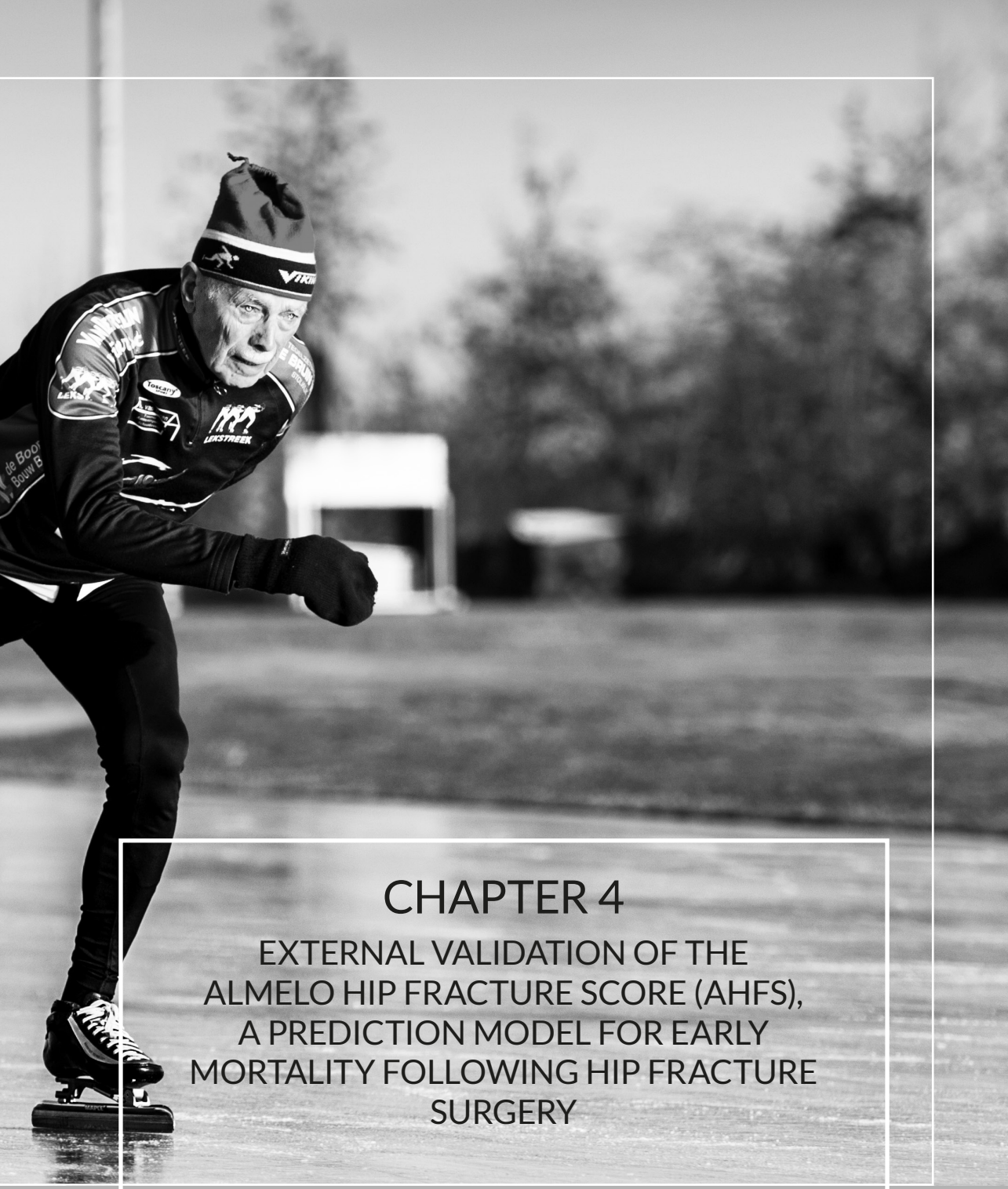

CHAPTER 4

EXTERNAL VALIDATION OF THE ALMELO HIP FRACTURE SCORE (AHFS), A PREDICTION MODEL FOR EARLY MORTALITY FOLLOWING HIP FRACTURE SURGERY

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Submitted

Abstract

Introduction

Early mortality (<30 days) in hip fracture patients is as high as 10%. Several risk assessment tools have been developed to identify patients at high risk for early mortality. Among them the Almelo Hip Fracture Score (AHFS), that was developed recently and showed promising results. Up to date, this tool has not been validated, therefore we aim to perform an external validation of the AHFS.

Method

An external validation of the AHFS was conducted in a cohort of hip fracture patients (Delft cohort). Data was prospectively collected during admission. The AHFS score was calculated for all patients over 70 years of age admitted with a hip fracture in our hospital. The characteristics of the Delft Cohort, sensitivity, specificity, positive predictive value, negative predictive and area under the curve were calculated and compared to the original Almelo cohort.

Results

422 patients of 70 years and older were included. Mortality within 30 days was 7.6%. For the high-risk cut-off point specificity was 95.4% and sensitivity was 28.1%. Specificity in the Almelo cohort was 92.5% and sensitivity 42.2%. The area under the ROC curve was 0.70 (95% CI 0.60 – 0.79).

Conclusion

This external validation showed that the AHFS was acceptable and comparable to the values in the Almelo cohort. We think that this score can be used to identify patients at high risk for early mortality.

Introduction

Hip fractures are very common among elderly, every year 1.6 million people are affected worldwide. With the current urbanization and ageing of the world's population this number is expected to grow to an even bigger number. Estimations vary between 7.3 and 21.3 million by 2050. [1, 2] Fractures of the hip have a serious effect on mortality and morbidity. The morbidity of hip fractures leads to 2.9 million disability adjusted life years in the world [3]. The mortality rate within the first 30 days is 10% and reaches up to 33% one year after surgery [4]. To be able to decrease (early) mortality it is important to correctly identify patients at high risk of early mortality.

Throughout the years, several risk assessment tools have been developed to predict early mortality [5]. The Association of Anesthetists of Great Britain and Ireland have developed the Nottingham Hip Fracture Score (NHFS), which is known as the most optimal screening tool so far [5, 6]. However, it has limited discriminative power [7]. The NHFS contains the abbreviated mental test score (AMTS), which can be time consuming and challenging to obtain in an emergency setting [8]. Therefore, the Almelo Hip Fracture Score (AHFS) was developed in the Netherlands [9]. The first results of this prediction model are promising and suggest higher specificity and sensitivity in assessing early mortality among the elderly with a hip fracture [9]. The AHFS is a more extensive and faster to obtain risk model than the NHFS. The score has two important extra variables to the original NHFS; the Parker Mobility Score and the ASA classification. The variable AMTS was replaced by cognitive frailty (yes/no), to make it easier and faster to obtain. The aim of this study is to perform an external validation of the AHFS.

Methods

Patients

We conducted a prospective observational cohort study of 525 hip fracture patients. The study did not fall under the scope of the medical research with human subject act (WMO), therefore ethical approval was not required. Information of our study for patients, or family members, was provided in a binder specially designed for hip fracture patients in our hospital. (10) All hip fracture patients were admitted to the emergency department of a 450-bed teaching hospital (Delft, the Netherlands) between January 2008 and December 2009. Patients with a fracture due to a high-energy trauma or with a pathologic fracture and patients younger than 70 years (n=103) were excluded. This cohort will be named the 'Delft cohort'. Length of follow-up was at least 3 months or until death occurred.

The AHFS was developed using data of 850 hip fracture patients aged 70 years and older admitted to the Trauma Surgery department at Hospital Group Twente (ZGT) between April 1, 2008, and October 23, 2013(10). Patients with a pathological or periprosthetic fracture were excluded, as well as patients who were referred to the orthopedic department, due to an indication for total hip replacement, and patients who died preoperatively. This cohort will be named the Almelo cohort.

Data collection

Data were collected uniformly and recorded by a standard evaluation form on the date of admission. [10]. Demographic data prospectively collected were age and sex. On admission the following clinical characteristics were prospectively obtained: serum haemoglobin measured in gram /decilitre, cognitive frailty defined as dementia (diagnosed by neurologist or geriatrician), cognitive disorders or delirium on admission. Living in an institution prior to the fracture was based on history taking. Retrospectively the hospital information system was checked to obtain data on the number of comorbidities and history of malignancy at the time of admission. The Parker Mobility Score (PMS) represents the level of mobility before fracture [11]. The total score ranges from 0 (not able to walk) to 9 (fully independent). The American Society of Anaesthesiologists Physical Status classification (ASA) was determined by the anaesthesiologist prior to surgery (range 1-4) [12]. Outcome was measured as mortality within 30 days following the hip fracture, this was defined as early mortality [9]. Mortality data was obtained from population registers of the counties as well as the hospital's information system at 30 days after hip fracture. Survival is considered as survival of 30 days or longer after hip fracture.

The AHFS score assesses the risk of early mortality following hip fracture in patients aged ≥70 years. The risk model consists of 9 variables: age, sex, admission serum haemoglobin, cognitive frailty, living in an institution, numbers of comorbidities, malignancy, Parker Mobility Score and ASA score (table 1). Between 0 and 7 points are scored for each variable based on the rounded-up beta coefficients associated with the original multivariate logistic regression. Data was transformed into a simple score ranging from 3-19 to predict the risk of early mortality (Table 1). The developers of the AHFS used a cut off score ≥ 13 to identify the high risk of early mortality group [9]. A cut-off point of AHFS ≤ 9 was set for the low risk group.

Table 1. Risk score form of the Almelo Hip Fracture Score

Age	≤86 years	4 points
	70-85 years	3 points
Sex	Male	1 point
	Female	0 points
Admission serum hemoglobin	≤ 10 g/dl	1 point
	> 10 g/dl	0 points
Cognitive frailty	Yes	1 point
	No	0 points
Living in an institution	Yes	1 point
	No	0 points
Number of comorbidities	≥2	1 point
	< 2	0 points
Malignancy	Yes	1 point
	No	0 points
Parker Mobility Score	≤ 5	2 points
	> 5	0 points
ASA Score	1-2	0 points
	3	3 points
	4	7 points
Sum of points		… points

Statistical analysis

Baseline characteristics in each group were collected and tested for normality using a Shapiro-Wilk test. Continuous data are shown as median with the interquartile range (IQR), in case of a non-parametric distribution. Categorical data are presented as the absolute number of subjects in each group, along with the percentages. Differences in non-parametric distributed continuous data between groups were assessed using a Mann-Whitney U-test. Categorical data were analyzed using a Chi-square or Fisher's exact test. Sensitivity analysis was performed using the original cut-off points for the AHFS of 9 and 13 (9). There was no missing data in this cohort. A receiver operating characteristics (ROC) curve was plotted by the sensitivity versus the 1-specificity. The area under the curve (AUC) was measured and the Hosmer-Lemeshow test was performed to assess the overall calibration error. All statistical analyses included two tailed tests. A P-value of 0.05 was considered to indicate statistical significance. SPSS statistics package version 24.0 for Mac (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

A total of 422 patients were included. Baseline characteristics are described in table 2. The median age was 84.3 (IQR 79.3-89.0; range 70.3 – 101.0) years,

75.4% were female. 7.6% patients (n=32) died within 30 days after the hip fracture. Patients in the early mortality group were older (86.9 years vs. 84.1 years, *p*=0.036) and physically frail; they had a higher ASA classification, more comorbidities (>2 comorbidities 84.4% vs. 57.2%, *p*=0.002) and lower mobility scores (PMS< 5 75,0% vs. 50,0%, *p*=0.009). Less patients were institutionalized before admission in the early mortality group (21.9%) compared to the survival group (45.1%) *p*=0.015.

Table 2 Baseline characteristics

Characteristics	**All patients Delft (n=422)**	***All patients Almelo (n=850)***	**Early mortality Delft group (n=32)**	**Survival group Delft (n=390)**
Age at time of admission (years)	84.3 (79.3-89.0)	*83.0*	86.9 (81.2-93.4)	84.1(79.2-88.8)*
AHFS				
Age ≥ 86 years	181 (42.9%)	*323 (38.0%)*	16 (50%)	165 (42.3%)
Sex (male)	104 (24.6%)	*224 (26.4%)*	6 (18,8%)	98 (25.1%)
Serum haemoglobin < 10 g/dl	31 (7.3%)	*52 (6.1%)*	3 (9.4%)	28 (7.2%)
Cognitive frailty	112 (26.5%)	*293 (34.5%)*	11 (34.4%)	101 (25.9%)
Living in an institution	183 (43.4%)	*249 (29.3%)*	7 (21.9%)	176 (45.1%) *
≥ 2 comorbidities	250 (59.2%)	*450 (52.9%)*	27 (84.4%)	223 (57.2%) *
History of malignancy	64 (15.2%)	*207 (24.4%)*	5 (15.6%)	59 (15.1%)
PMS ≤ 5	219 (51.9%)	*376 (44.2%)*	24 (75%)	195 (50.0%) *
ASA 1-2	269 (63.7%)	*184 (21.7%*	11 (34.4%)	258 (66.2%)
ASA 3	128 (30.3%)	*553 (65.1%)*	13 (40.6%)	115 (29.5%)
ASA 4	25 (5.9%)	*113 (13.3%)*	8 (25.0%)	17 (4.4%)
Total AHFS points	7 (5-10)		9.50 (7-13.8)	7 (5-9)*
Mortality	32 (7.6%)	*64 (7.5%)*		
Fracture type				
Femoral neck	241 (57.1%)	*443 (52.1%)*	17 (53.2%)	224 (57.4%)
Trochanteric	163 (38.7%)	*369 (43.4%)*	13 (40.7%)	150 (38.5%)
Subtrochanteric	18 (4.3%)	*38 (4.5%)*	2 (6.3%)	16 (4.1%)
Treatment				
Osteosynthesis	229 (54.3%)		16 (50.0%)	213 (54.6%)
Arthroplasty	181 (42.9%)		11 (34.4%)	170 (43.6%)
Conservative	12 (2.8%)		5 (15.6%)	7 (1.8%)

Continuous data are presented as median (interquartile range) and categorical data are described as frequency (percentage).

* Statistically significant difference between early mortality and survival group p <0.05

The AHFS was calculated for the Delft cohort, the results are shown in table 2. The median AHFS score was higher in the early mortality group 9.5 (IQR 7.0-13.8) compared to the survival group 7 (IQR 5-9) $p<0.001$. Table 3 and 4 show the results of the validity analysis of the high risk cut off point of 9 and lower and 13 and higher. Applying the low cut-off point the sensitivity was comparable (75.9% vs 78.1%) but specificity was lower (50.0% vs 72.5%) to the values found in the Almelo cohort. In the high cut-off point sensitivity (28.1 vs. 42.2%) was lower, but specificity (95.4 vs. 92.5%) was comparable to the Almelo cohort.

Table 3 mortality and survival in the different risk groups according to the AHFS

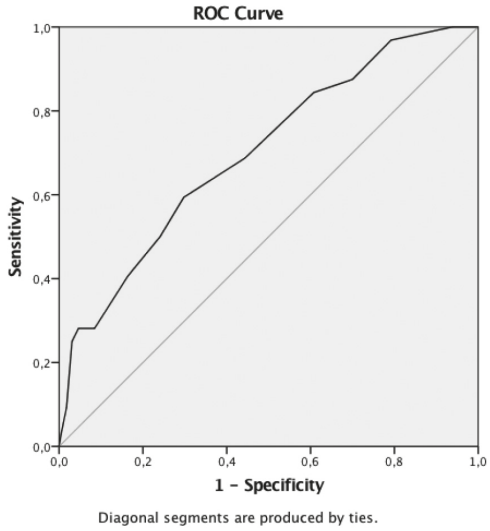
	Survived	**Died within 30 days**	**Total**
AHFS low risk (≤ 9)	296	16	312
AHFS intermediate risk (10 -12)	76	7	83
AHFS high risk (≥13)	18	9	27
Total	390	32	422

Table 4 Results of the validity analysis of the high risk AHFS for early mortality for the cut-off point of 9 and lower and 13 and higher.

	AHFS low risk ≤ 9		**AHFS high risk ≥13**	
Characteristics	Delft cohort	Almelo cohort	Delft cohort	Almelo cohort
Sensitivity	75.9%	78.1%	28.1%	42.2%
Specificity	50.0%	72.5%	95.4%	92.5%
Positive predictive value	14.5%	18.8%	33.3%	31.4%
Negative predictive value	94.9%	97.6%	94.2%	95.2%
Likelihood ratio Positive	1.51	2.35	6.11	5.62
Likelihood ratio Negative	1.84	0.33	0.71	0.62
Correlation with early mortality			0.254	n/a

The area under the ROC curves of the AHFS in the Delft cohort was 0.70 (95% CI 0.60-0.79) (**Figure 1**). The AHFS model showed a good fit between predicted and observed values (Hosmer-Lemeshow test, $p>0.76$).

Figure 1. The curved line shows the ROC curve of the Delft cohort. The diagonal indicate results no better than chance.



Discussion

The aim of this study was the external validation of the AHFS. We demonstrated that the validity of the score was generally comparable to the values found in the Almelo cohort. Therefore, we think that this score could be used to identify patients at high risk for early mortality within 30-days after hip fracture.

A high positive predictive value and high sensitivity are the most important features of a prediction model to correctly identify patients at risk. In the Delft cohort the positive predictive value was higher than in the Almelo cohort (33.3% vs. 31.4%). Sensitivity for the high cut-off point was higher in the Almelo cohort (42.2% vs. 28.1%). Specificity is the ability to give negative results in negative cases. Specificity in the Delft cohort was similar to the Almelo cohort (95.4% vs. 92.5%). A high negative predictive value and high specificity are important to identify patients not at risk. This is important since we expect that low risk patients might not receive the close monitoring compared to the high-risk patient. The negative predictive value for the low cut-off point was comparable to the Almelo cohort (94.9% vs 97.6%). In the Delft cohort specificity was larger than in the Almelo cohort (75.9% vs 72.5%). Together these items resulted in a lower area under the curve in the Delft cohort than in the Almelo cohort (0.70 vs 0.80). In the Delft cohort more patients were classified ASA I and II than in the Almelo cohort (63.7% vs. 22%), this resulted in a lower overall AHFS score. The observed ASA I and II classification

is considerably high in the Delft cohort compared to large international studies that showed a prevalence of 39-43% [13-15] and a large study conducted in the Netherlands showed that 40% of the hip fracture patients were classified as ASA I or II [16]. Therefore, the current low prevalence of ASA I and II patients could possibly affect the correct prediction with the original cut-off points used [9]. Despite these differences and consecutive possible underestimation, the current AUC is still considered to be acceptable [9, 17].

The mortality rate after hip fracture in elderly patients ranges between 10% at 30 days up to 33% after one year [4]. These poor outcomes highlight the importance for a valuable mortality prediction model after hip fracture surgery. First of all, to target care to the ones who need it the most. Throughout the years successful methods to decrease mortality have been published. The orthogeriatric care model is an indicative example, in this model a patient is treated using a multidisciplinary approach involving both an orthopaedic surgeon and a geriatrician [18]. In the orthogeriatric care model a 40% mortality decrease was observed in the first 30 days after hip fracture. (6) Methods to identify patients who benefit most from these expensive treatment regimens are scarce and risk scores like the AHFS can be of important use. More accurate risk scores are also helpful in shared decision making as well as patient- and family education. Recently a study was started to guide very frail patients (ASA 4-5 or not able to ambulate independently) and their family in the choice between surgery and palliative treatment. (www.frail-hip.nl) In order to guide this treatment decision, it is important to have tools to predict outcome on an individual patient level, based on larger population studies. The AHFS might be such tool to help clinicians guide this process.

Throughout the last years there is a growing number of proposed prediction models. Moreover, these prediction models are increasingly used in clinical guidelines [19]. Before prediction models can be used in clinical practice it is important that its predictive performance is empirically evaluated in a dataset that is different to the one used to develop the model (external validation) [20, 21]. As far as we are concerned, we are the first to externally validate the AHFS prediction model. A large external validation study showed that five mortality prediction models (amongst those NHFS) had an acceptable AUC in a hip fracture patient cohort [5]. However, this study reported large amounts of missing data and thereby changes made in the original models, which was due to its retrospective nature [5]. The AUC in the five studies varied between 0.69 and 0.77 and was comparable to what we observed. This implicates that that the AHFS is a valuable

risk assessment tool. A smaller external validation study of six different models found that none of the tested models had excellent discriminative power, defined as AUC > 0.80, with AUCs ranging from 0.43 to 0.68 [22]. The development cohort of the AHFS, did show an excellent discriminative power with an AUC of 0.82. Karres *et al* concluded that so far the NHFS showed the most promising results with reasonable discrimination [5]. A negative point however, is the use of the AMT which can be complicated and time consuming among cognitive impaired elderly people. By contrast, the AHFS is a more extensive but easier to obtain risk score using only cognitive frailty as a variable. Therefore, in the clinical setting the AHFS might not only be one of the best discriminative, but also easy and quicker to obtain than the current ones available.

The present study has some limitations that should be considered. First, the number of patients included in this cohort. Although 422 is a considerable number, 33 events (mortality within 39 days) is small to perform an external validation [23]. However, the reported mortality rates between the original and validation cohort was similar. Second, the variables comorbidities and history of malignancy were retrospectively collected. Nevertheless, there was no missing data on these variables after extensive investigation in the electronic patient information system. Moreover, all other patient characteristics were collected prospectively resulting in absolute completeness of data.

In conclusion, we showed that the AHFS can predict mortality as accurate as was suggested by Nijmeijer et al.[9]. The AHFS is a reliable, feasible and easy-to-use instrument to predict 30-day mortality after hip fracture surgery. A better prediction of patients at risk may be beneficial in reducing the high early mortality rate after hip fracture surgery. Moreover, the model may also be useful in managing expectations and education of hip fracture patients- and their families.

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CHAPTER 5

DELIRIUM RISK SCREENING AND HALOPERIDOL PROPHYLAXIS PROGRAM IN HIP FRACTURE PATIENTS IS A HELPFUL TOOL IN IDENTIFYING HIGH-RISK PATIENTS, BUT DOES NOT REDUCE THE INCIDENCE OF DELIRIUM.

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Abstract

Introduction

Delirium in patients with hip fractures lead to higher morbidity and mortality. Prevention in high-risk patients by prescribing low dose haloperidol is currently under investigation.

Methods

In this prospective cohort surveillance, hip fracture patients were assessed for risk of developing a delirium with the Risk for Delirium (RD) score. High-risk patients (score ≥5 points) were treated with a prophylactic low dose of haloperidol according to hospital protocol. Primary outcome measurement was incidence of delirium. Secondary outcomes were differences between high- and low-risk patients in delirium, length of stay, return to pre-fracture living situation and mortality. Logistic regression analysis was performed with age, ASA-classification, known dementia, having a partner, type of fracture, institutional residence and psychotropic drug use as possible confounders.

Results

445 hip fracture patients aged 65 years and older were admitted from January 2008 till December 2009. The RD-score was completed in 378 patients, 173 (45.8%) patients were identified as being at high risk for development of a delirium and treated with prophylactic medication. Sensitivity was 71.6%, specificity 63.8% and the negative predictive value of a score < 5 was 85.9%. Incidence of delirium in our study cohort (27.0%) was not significantly different compared to 2007 (27.8%) 2006 (23.9%) and 2005 (29.0%) prior to enrolling the RD- protocol. Logistic regression analysis showed that high-risk patients did have a significant higher delirium incidence (42.2% vs. 14.1%, OR 4.1, CI 2.43-7.02). They were more likely to be living at an alternative situation after 3 months (62.3% vs. 17.0%, OR 6.57, CI 3.23-13.37) and less likely to be discharged from hospital before ten days (34.9% vs. 55.9%, OR 1.63, CI 1.03-2.59). Significant independent risk factors for a delirium were a RD-score ≥5 (OR 4.13, CI 2.43-7.02), male gender (OR 1.93, CI 1.10-3.39) and age (OR 1.03, CI 0.99-1.07).

Conclusion

Introducing the delirium prevention protocol did not reduce the incidence of delirium. The RD-score did identify patients with a high-risk to develop a delirium. This high-risk group had longer length of stay and less return to pre-fracture living situation. The negative predictive value of a score < 5 was high, as it should be for a

screening instrument. Concluding, the RD-score is a useful tool to identify patients with poorer outcome.

Introduction

Delirium is a common and serious complication in hip fracture patients. It leads to lower functional abilities, longer hospital stay, impaired cognitive function, more admissions to long term special care facilities and higher mortality rates [1–5]. This advocates the importance of preoperative delirium risk assessment.

Reported post-operative incidence rates range widely from 16 till 62% [6]. This broad range can be explained by the patient inclusion criteria and different scoring methods for delirium. Furthermore, delirium is frequently undetected or misdiagnosed [7]. Haloperidol is widely used for the symptomatic treatment of delirium. However, prophylaxis with haloperidol did not lower delirium incidence, it did reduce duration of episodes and the severity in a recent randomized controlled trial [8].

In 2008 we introduced an integrated hip fracture pathway that included a Risk Model for Delirium [9]. This model should identify high-risk patients that are subsequently prescribed prophylactic haloperidol. Primary purpose of this surveillance study was to determine whether using prophylaxis would diminish delirium incidence in hip fracture patients. The second aim was to investigate the value of the score and differences between low and high-risk patients (as determined by the risk model) in delirium incidence, length of stay, return to pre-fracture living situation and mortality.

Methods

A surveillance study was conducted on a series of consecutive admissions for a hip fracture to a 450-bed teaching hospital in Delft, the Netherlands.

Patients

From January 2008 to December 2009, all our consecutive admissions for a hip fracture were registered and prospectively studied with respect to presence of delirium. Thus 529 admissions for a hip fracture (522 patients) were recorded. These were all patients with a fracture due to a low-energy trauma and of non-pathologic origin. For this study, only patients of 65 years and older (445 patients) were included for evaluation. Duration of follow-up was 1 year. The control group for evaluating the effect of the use of the RD was a historic consecutive series

of 611 hip fracture patients of 65 years and older admitted between 2005-2007, prior to enrolling our RD protocol. As this study is an evaluation of our delirium protocol, it is considered to be a "Post Marketing Surveillance". Therefore, approval of a medical ethical committee was not necessary.

Assessment measures

Uniformed data collection of all patients was achieved by evaluating all patients on admission in a standard procedure and recording, according to our local hip fracture protocol [9]. The following data was collected of all patients; age, gender, having a partner, history of dementia, RD-score, pre-fracture living situation, ASA classification [10], psychotropic drug medication, type of fracture, treatment and anaesthesia, in-hospital complications, discharge location, in hospital mortality and length of stay (LOS). Diagnosis of delirium was based on criteria of the DSM IV [1]. Patients were observed for these criteria by both doctors and nursing staff during their daily rounds and assessments. When signs of delirium were notified, they were recorded in the medical and nursing records. Delirium incidence in this series was scored based on these medical and nursing staff records, directly after discharge. Living situation was assessed at 3 months post-admission by questionnaires sent to all patients. Mortality was assessed until 1 year after hospitalisation, using the digital registration system of the hospital. Delirium incidence in the historic group (2005-2007) was drawn from our hip fracture database that was built retrospectively by evaluation of the patients' files and complication register.

Assessing the risk for a delirium at admission, using The Risk Model for Delirium (RD, figure 1), is a standard part of our local hip fracture protocol [9]. This model was developed in 2004 by the department of Psychiatry in our hospital and uses predisposing risk factors for delirium that were weighted, based on known literature at that moment [11–17]. The model was designed with a cut-off point of 5; patients scoring 5 or more points were considered high-risk patients. For this group delirium prophylaxis is prescribed, being 2 times a day 1 mg of Haloperidol. In the case of contra-indications for the use of Haloperidol, like Parkinson's disease or Lewy-body dementia, alternative prophylaxis was started. When patients developed a delirium, they were fully assessed to exclude a somatic cause and treated by the psychiatric department. The RD-score and the delirium protocol were implemented fully on the departments of Orthopaedics and Trauma surgery in 2008, as a part of the integrated hip fracture care pathway.

The current cohort was analysed for differences between low- (<5) and high-risk (≥5) patients for delirium incidence, length of stay (LOS), alternative living situation (ALS) 3 months post-fracture (compared to the pre-fracture situation) and in-hospital, 3- and 12-month mortality.

Statistical analysis

Categorical data are presented as the number of subjects, along with the percentages. Continuous data are presented as means with standard deviations (SD). The value of the RD-score was evaluated using sensitivity, specificity, the negative predictive value of a low score and the positive predictive value of a high score. Chi-square test, Fisher's exact test and independent Student's t-test were used as applicable for univariate analysis. A P-value lower than 0.05 was taken as the threshold of significance. LOS was divided in two groups at the level of the median (10 days).The ability of the RD to discriminate was estimated by the receiver-operating characteristic (ROC) curve. Univariate analysis was followed by multivariable logistic regression to test the association between the RD and delirium, mortality (in-hospital, 3 and 12-month), LOS, and ALS at 3 months. In these analyses age, gender, ASA score (I/II versus III/IV), psychotropic drug use, institutional residence and known dementia were seen as possible confounders. The analysis regarding return to the pre-fracture living situation was performed on patients that lived independent at home before they broke their hip. To this analysis 'having a partner' was added as an extra possible confounder. The likelihood ratio backward test was conducted to find the best-fit model by selecting the variables one by one. The probability for entry was set at 0.05, and the probability for removal at 0.10. All data were analysed with SPSS 17.0 (SPSS Inc. Chicago, USA)

Table 1. The Risk Model for Delirium

Predisposing risk factors for delirium	Points
Delirium during previous hospitalisation	5
Dementia	5
Clock drawing (displaying 10 past 11)	1
- Small mistakes	2
- Big mistakes, unrecognizable or no attempt	
Age	1
- 70 till 85 years	2
- Older than 85 years	
Impaired hearing (patient is not able to hear speech)	1
Impaired vision (vision less than 40%)	1
Problems in activities of daily live	0.5
- Domestic help, or help with meal preparation	0.5
- Help with physical care	
Use of heroin, methadone or morphine	2
Daily consumption of 4 or more alcoholic beverages	2
Total score	

Results

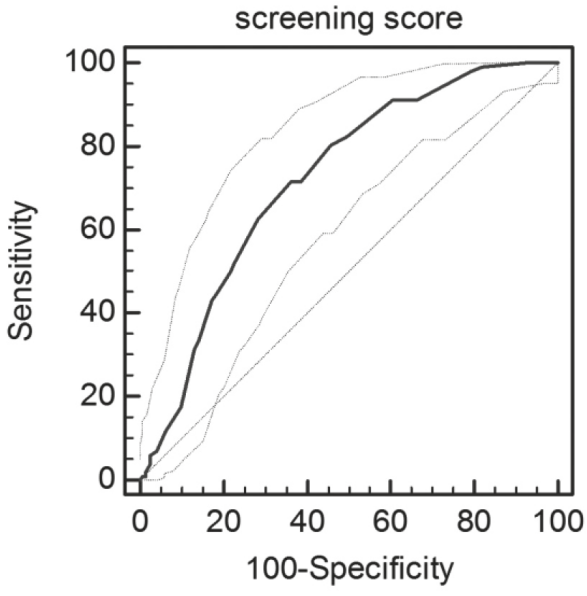
In 378 patients (85%) the RD-score was completed correctly. Delirium was diagnosed in 102 of these 378 patients (27.0%). Due to the inability of patients to participate or a patient-to-nurse ratio that was too high at some moments, the RD-score was incomplete or not performed in 67 patients. These 67 discarded patients, as of an incomplete RD-score, had a delirium incidence of 28.4%, not significantly different from study cohort (p= 0.816). Furthermore, there was no difference in age (82.4 vs. 83.8 years; p=0.168), nor LOS (15.0 vs. 13.2 days, p=0.172) and 1-year mortality (35.8% vs. 24.9%, p=0.061) between the completed RD and non-completed RD-score groups.

The mean age of the prospective cohort 2008-2009 (83.7 years) was not significantly different from the historical cohort 2005-2007 (82.9 years) (P = 0.082) The percentage of male patients was 26.2% in the prospective cohort and 24.3% in the historical cohort were the same as well (P = 0.515). No significant differences in delirium incidence were found between the prospective 2008/2009 (27%) and the historic hip fracture cohorts; 2005 (29.0%, P=0.28), 2006 (23.9%, P=0.81) and 2007 (27.8%, P=0.44). (Chi Square - test)

The protocol was violated in 49 out of 378 patients (13%); prophylaxis was not started in 26 patients with a score of ≥5 and was started in 23 patients scoring <5.Delirium incidence in the 23 low-risk patients was 34.8%, significantly higher than in the 182 that were not prescribed prophylaxis, 11.5%. (Pearson Chi-Square, p=0.003). Delirium incidence in the 26 high-risk patients not started on prophylaxis was 50.0%, not significantly higher than in the 147 that were prescribed prophylaxis, 40.8%. (Pearson Chi-Square, P=0.38) When the protocol violations were excluded, high-risk patients still had a higher risk of delirium (P<0.001), a longer LOS (P<0.001) a higher likelihood of living at an alternative living situation after 3 months (P=0.001) and higher mortality rates at 3 and 12 months (P<0.001).

A receiver-operating characteristic (ROC) curve, displayed in figure 1, made of the continuous outcome of the RD-score showed an area under curve of 0.722 (CI 0.674 - 0.767, p<0.0001). The best cut- of-point for balancing the sensitivity and specificity was 5, corresponding with the pre-study chosen cut-off point. Sensitivity of the cut-off point of 5 was 71.6% (73/102), specificity was 63.8% (176/276). Excluding patients who were not treated according to the protocol, the sensitivity became 74.1% (60/81) and the specificity 64.9% (161/248). The negative predictive value of a score < 5 (i.e. no delirium) was 85.9% (176 / 205), the positive predictive value for a score of 5 and more (i.e. delirium) was 42.2% (73 / 173)

Figure 1 ROC curve of the RD-score with 95% confidence intervals. The diagonal indicate results no better than chance



Specific details of 205 low-risk (score < 5) and 173 high-risk (score of ≥ 5) patients are shown in table 2. High risk patients were significantly older, more often female, suffering from dementia, ASA classification III-IV, having no partner, residing in an institution, using psychotropic drugs and receiving spinal/epidural anaesthesia during surgery. At univariate analysis (table 2), patients with a RD-score of ≥ 5 had a higher risk for a delirium, (P<0.001). Furthermore, they had a longer LOS, a higher chance of living at an alternative living situation after 3 months and a higher 3- and 12-month mortality rate (all P<0.001). Multivariable analysis per outcome variable is displayed in table 3. The RD-score was a significantly contributing variable for delirium, length of stay and alternative living situation at 3 months. Age was a strong independently contributing variable as well, as was ASA-classification.

Table 2: Relative risks for different demographic characteristics and outcome parameters with a RD- score ≥5 (univariate analysis)

	Score ≥5 (n = 173)	**Score <5 (n=205)**	**Relative risk (CI)**	**P value**
Age, mean ± SD	86.6 ± 6.5	81.4 ± 7.1	n/a	<0.001[a]
Female n (%)	137 (79.2%)	142 (69.3%)	1.35 (1.01-1.80)	0.029
Dementia n (%)	89 (51.4%)	0 (0%)	3.44 (2.87-4.12)	<0.001
ASA -III-IV n (%)	79 (45.7%)	47 (22.9%)	1.68 (1.36-2.07)	<0.001
Institutional residence n (%)	107 (61.8%)	21 (10.2%)	3.17 (2.54-3.95)	<0.001
Having no partner n (%)	119 (79.3%)	123 (60.9%)	1.74 (1.26-2.41)	<0.001
Psychotropic drug use n (%)	89 (51.4%)	50 (24.4%)	1.82 (1.47-2.25)	<0.001
Fracture type				
- neck of femur	115 (56.1%)	102 (59.0%)		0.854[b]
-(inter) trochanteric	81 (39.5%)	64 (37.0%)	0.95 (0.78-1.15)	0.592[c]
-subtrochanteric	9 (4.4%)	7 (4.0%)		
Treatment				
- osteosynthesis	124 (60.5%)	87 (50.3%)		0.077[b]
-(hemi-) arthroplasty	79 (38.5%)	81 (46.8%)	1.19 (0.98-1.44)	0.072[c]
-conservative	2 (1.0%)	5 (2.9%)		
Spinal/epidural anesthesia	198 (97.5%)	153 (91.1%)	2.26 (1.05-4.85)	0.006
Delirium	73 (42.4%)	29 (14.1%)	1.98 (1.62-2.41)	<0.001
Length of stay ≥ 10 days	110 (65.1%)	90 (44.1%)	1.61 (1.27-2.05)	<0.001
Alternative living situation at 3 months*	33 (62.3%)	28 (17.0%)	4.25 (2.65-6.80)	<0.001
In-hospital mortality	10 (5.8%)	4 (2.0%)	1.60 (1.12-2.26)	0.050
3-month mortality	40 (23.1%)	17 (8.3%)	1.69 (1.37-2.10)	<0.001
12- month mortality	64 (37.0%)	30 (14.6%)	1.77 (1.45-2.17)	<0.001

* Only calculated for the patients not yet living in institutions (n=218, n=32 missing)
[a] Independent t-test [b] Comparing 3 treatment groups; [c] RR and p-value comparing femur neck with (inter) trochanteric fractures and osteosynthesis with arthroplasty; CI=confidence interval

Table 3 Results of the multivariable logistic regression analysis per outcome variable

Outcome variable	Independent variables	Odds ratio	95% CI	P value
Delirium	Screening score ≥ 5	4.13	2.43 to 7.02	<0.001
	Age in years	1.03	0.99 to 1.07	0.082
	Male gender	1.93	1.10 to 3.39	0.022
Length of hospital stay ≥ 10 days	Screening score ≥ 5	1.63	1.03 to 2.59	0.037
	Age in years	1.06	1.03 to 1.10	<0.001
	ASA III-IV	1.55	0.97 to 2.47	0.069
Alternative living situation at 3 months	Screening score ≥ 5	6.57	3.23 to 13.37	<0.001
	Age in years	1.09	1.04 to 1.06	0.001
In-hospital mortality	Age in years	1.14	1.03 to 1.26	0.014
	ASA III-IV	3.83	1.13 to 13.0	0.031
	Institutional residence	3.54	0.89 to 14.0	0.072
3-month mortality	Age in years	1.11	1.05 to 1.17	<0.001
	ASA III-IV	2.48	1.33 to 4.61	0.004
	Institutional residence	2.97	1.55 to 5.68	0.001
12-month mortality	Age in years	1.08	1.03 to 1.12	0.002
	ASA III-IV	2.78	1.60 to 4.84	<0.001
	Having no partner	2.22	1.07 to 4.61	0.033
	Institutional residence	2.06	1.16 to 3.68	0.014

Female, having a partner, ASA I-II, screening score <5, not residing in an institution are reference categories

Discussion

Identification of hip fracture patients at risk for a delirium is important in order to start early treatment with medication and psycho-geriatric consultation. Therefore, it is of great value to have an accurate screening instrument. We used the Risk Model for Delirium (RD-score) to identify patients at risk for delirium and started prophylactic haloperidol in the high-risk group. Large differences between high- and low-risk patients regarding delirium incidence, length of stay, discharge location and mortality were anticipated. However in this study, prophylactic treatment of patients at high-risk for a delirium as identified by our RD-score, did not reduce incidence of delirium compared to our historical data. The score did identify patients with poorer outcome regarding delirium incidence, length of stay and return to pre-fracture living situation.

The RD-score had a moderate sensitivity (71.6%) and specificity (63.8%), this is in accordance with other risk models [18]. The negative predictive value of a score < 5 was quite high (85.9%), which is very important as a screening instrument

should have a high NPV. The consequence of a false positive test (i.e. prophylactic treatment with low-dosis haloperidol in a non-delirious patient) is in general modest as very few side effects of a low dose of haloperidol can be expected. Therefore its moderate positive predictive value (42.2%) is of lesser importance.

The pre-study chosen cut-off value for the RD-score of 5 was confirmed to be right by the ROC curve analysis. The cut-off provided a high-risk group with a significant higher relative risk of developing a delirium; OR (adjusted for age and gender) 4.13 (CI 2.43-7.02). Higher age and ASA classification, more residing in an institution and absence of a partner suggested a higher vulnerability of the high-risk group. This is demonstrated in outcome; high-risk patients had a longer hospital stay, a higher 3- and 12- month mortality, and a higher risk of staying at an alternative living situation 3 months after admission at univariate analysis. In multivariable analysis, the effect of the RD-score for mortality disappeared.

Several authors described a model that tried to identify high-risk patients for a delirium. One study used a cohort of vascular surgery patients [18], another major elective (non-cardiac) surgery patients [15] and 4 others used a cardiac surgery cohort [19–22]. All these models contained items that were not applicable to our patients, while they were patient group specific and designed for an elective surgery population. Kalisvaart et al [8] used a population that contained both elective hip surgery patients and hip fracture patients. They used visual impairment, disease severity (expressed by the Apache II score) [23], mental impairment (Mini Mental State Examination, MMSE) [24] and dehydration (expressed by blood urea nitrogen and creatinine ratio) as parameters. We chose to develop a simpler model that was easy to use in an acute admission, to achieve maximum use in daily practice. This has been accomplished; 85% of all patients had a complete RD-score. Despite the integration of the RD in a standard patient file, the delirium prophylaxis protocol was violated in 13% of patients. High turnover of doctors in the emergency department may have contributed to these violations.

Older age, cognitive impairment, use of psychopathologic drugs, functional impairment (both in daily activity and clock drawing) visual and hearing impairment were all included parameters that were found to be associated with delirium in a systematic review by Dasgupta et al [25]. Besides these, they found depression, psychopathologic symptoms, psychotropic drugs, institutional residence and medical co-morbidity to be important risk factors for a delirium. We used institutional residence as a possible confounder in regression analysis, which was

of non-significant contribution to the risk for delirium. However, it was a strong predictor of mortality at 3 and 12 months. Psychotropic drug use was associated with a screening score ≥ 5, but not a predictor of delirium or other outcome in multivariable analysis in our series. Based on our analysis, adding the factor "male gender" to the RD-score might improve its efficacy as this was a significant contributor to delirium (OR 1.93). This in contrast to findings by Dasgupta et al [25], who found no correlation between male gender and presence of a delirium. Twenty-three low-risk patients were prescribed haloperidol prophylaxis, against the protocol. This group had a higher percentage of delirium than the rest of the low-risk group, which was not hypothesized. The doctor that prescribed haloperidol against protocol might be triggered by patient factors that are not taken into consideration by the score but that do predispose to a delirium as they have a higher delirium incidence.

The prospective study design, the large sample size and the use of a predefined risk-stratification model are important issues for the interpretation of our study results. The main limitations are the subjectivity of determining a delirium and mental impairment of the patient. In our study, delirium was diagnosed based on clinical examination, as stated in the DSM IV [1]. We did not use a measuring instrument like a Confusion Assessment Method [7] to establish delirium. A second limitation was, that in cognitively impaired patients it is difficult to distinguish between delirium and cognitive impairment. Futhermore, patients were scored for known dementia based on history taking and information from digital patient files, a cognitive impairment score like the MMSE was not used [24].

Another limitation is the comparison of the delirium incidence in the whole cohort with the historical cohort. Ideally, we would have compared only the high-risk groups of both cohorts. However, we could not identify high-risk patients in the historical group as the RD-score was implemented fully in 2008. We did demonstrate that both cohorts were comparable regarding mean age and number of male patients, being the main risk factors in the multivariable analysis of the prospective cohort, besides a high RD-score. Therewith one could have observed a decline in delirium incidence due to prophylaxis with haloperidol.

Haloperidol is widely used for the symptomatic treatment of delirium, as prophylaxis it has a more disputable reputation. In one small study in gastrointestinal surgery patients, haloperidol prophylaxis proved to be effective in reducing delirium incidence [26]. However, a large study in hip fracture patients [8] did not support

this finding. Our protocol was developed with the intention to reduce delirium incidence by earlier identification of the patients at risk with an objective scoring system, the RD-score. Compared to our historic data, however, we saw no decline in the incidence of delirium. This corresponded with a recent Cochrane review [27] on interventions preventing delirium. It stated that pro-active geriatric consultation could reduce delirium incidence, but that low-dose haloperidol prophylaxis did not diminish delirium rates [27]. Kalisvaart et al. [8] showed that low-dose haloperidol prophylaxis can reduce severity and duration of delirium and that this may shorten length of stay. During the study period, we started using the Delirium Observation Scale [28] to monitor depth and duration of the delirium. However, this instrument was not yet used in a consistent way over the study period to take these data in account for this analysis. Further research should focus more on depth and duration of delirium instead of incidence, since this might give better inside in efficacy of prophylactic treatment. We believe that more emphasis should be given on non-pharmalogical interventions to prevent a delirium. These interventions include providing orientation with calendars, clocks and photographs and maintain day-night rhythm. However, they take valuable manpower from the nursing staff. When these interventions can be targeted to the high-risk group (as identified with the RD-score) it would be preferable

Conclusions

Prescribing prophylactic haloperidol to high-risk patients as identified by the Risk Model for Delirium did not reduce delirium incidence in a cohort of hip fracture patients. The RD-score did prove to be an accurate tool for identifying high-risk patients with poorer outcome regarding delirium incidence, length of stay and return to pre-fracture living situation.

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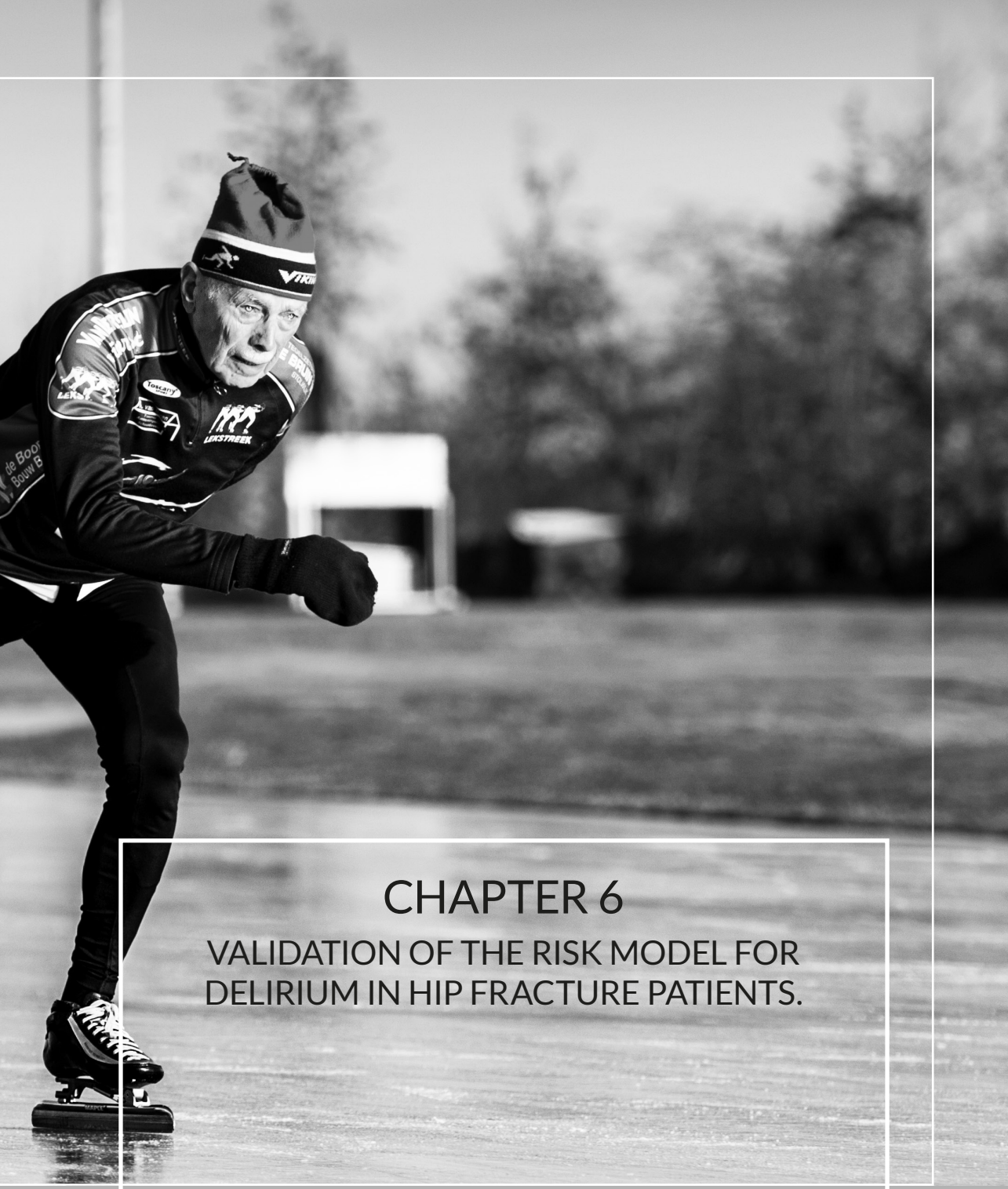

CHAPTER 6

VALIDATION OF THE RISK MODEL FOR DELIRIUM IN HIP FRACTURE PATIENTS.

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Abstract

Introduction:

The Risk Model for Delirium (RD) score is a 10-item questionnaire that allocates hip fracture patients after admission to hospital to be either at high or at low risk for delirium. This allows targeted preventive actions. Clinical reliability, validity and feasibility of the RD score are discussed.

Methods:

Demographic data, RD score and delirium incidence of all consecutive admissions for hip fractures in patients 65 years and older were collected. In 102 patients, the RD score was repeated. Interobserver reliability and validity were determined. The correlation between delirium and items both included and not included in the RD score was calculated.

Results:

A total of 378 patients were included; 102 (27%) were diagnosed with a delirium. The intraclass correlation coefficient of the RD score was 0.77 [confidence interval (CI) 0.68–0.84]. Sensitivity was 81.4% (71.4–87.6), and specificity was 56.2% (50.1-62.1). Area under the receiver operating characteristic curve was 0.73 (CI 0.68–0.77). A multivariable logistic regression analysis showed that besides the RDscore, a trochanteric fracture and male gender were independent risk factors for delirium.

Conclusion:

The RD score is a reliable, feasible and valid instrument for predicting delirium in hip fracture patients.

Introduction

Delirium in hip fracture patients is a serious complication, leading to higher morbidity and mortality [1–4]. A recent Cochrane review states that proactive geriatric consultation can reduce delirium incidence [5]. To optimize patient care, it is important to perform a preoperative risk assessment in order to target preventive interventions. This risk assessment should be simple and brief to increase participation of both patients and medical professionals. Several authors described a model that identifies patients at high-risk for delirium. These models were applied in cohorts of vascular surgery patients [6], elective (noncardiac) surgery patients [7] and four cohorts of cardiac surgery patients [8–11]. All these models contained items that are not applicable to hip fracture patients. On the contrary, these models are not only patient group specific, but are also designed for elective surgery patients. Kalisvaart et al. published the outcome of a risk score for delirium in a population that contained both elective hip replacement surgery and hip fracture patients [12]. They scored visual impairment, disease severity [using the Acute Physiology and Chronic Health Evaluation (APACHE) II score] [13], mental impairment [scored with the Mini Mental State Examination (MMSE)] [14] and dehydration (expressed by blood urea nitrogen– creatinine ratio). We chose to develop a simpler model that is easy to use in an acute admission setting to achieve maximum use in daily practice: the Risk Model for Delirium (RD) score. Recently, we published the results of the use of the RD score in daily practice [15]. This study evaluates the clinical reliability, validity and feasibility of the RD score in hip fracture patients.

Methods

Patients

All consecutive admissions for surgical treatment of a hip fracture to a 450-bed Dutch teaching hospital between January 2008 and December 2009 were registered prospectively. This was done as part of daily care and monitoring according to our local hip fracture protocol. [16] Patients of this cohort aged 65 years (n=445) and older were included in the current study. Sixty-seven patients were excluded because the RD score was not completed sufficiently. Final analysis was therefore performed in 378 patients with a mean (S.D.; range) age of 83.8 (7.3; 65–101) years; 279 (73.8%) were female. Failure to complete the RD score was mainly because of lack of time of medical personnel at the emergency department (ED) or refusal of patients to cooperate. The excluded patients had a delirium incidence of 28.4%, not significantly different from the included study cohort (27%,

P=.82). Furthermore, there was no difference in mean (S.D.) age between these groups [82.4 (7.4) vs. 83.8 (7.3) years; P=.17].

The following baseline characteristics were collected at admission: age, gender, presence of a partner, presence of dementia, prefracture living situation, American Society of Anaesthesiologists (ASA) physical status classification, psychotropic drug use (antidepressant, antipsychotic or any form of tranquillizer), RD score, type of fracture, hip fracture treatment, type of anesthesia and occurrence of a delirium during admission [17]. Presence of dementia was determined upon history taking from patients, families and caretakers. Ward nurses observe patients three times a day for clinical signs of a delirium as described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria[18] . Symptoms of a delirium were registered in both the medical and nursing staff records. Directly after discharge, both records were examined independently by two authors (S.M. and A.V.) to register prevalence of a delirium. In case of doubt (36 patients), a psychiatrist was consulted, who diagnosed a delirium in 27 patients.

RD score

The RD score was developed in 2004 by the department of Psychiatry of the Reinier de Graaf Hospital, Delft, the Netherlands. [15] At that moment, the most important known risk factors for a delirium were used in the RD score. [7, 19–24] Table 1 shows the score, its items and values assigned to the specific items. Predisposing, instead of precipitating factors were selected, while these are present at admission and more easy to use. Points assigned to each item are derived from the relative risk of that factor to develop a delirium. [7, 19–24] Based on the clinical experience, patients with a score of 5 or more points were considered to be high-risk patients. At admission at the ED, nurses (or doctors) filled out the RD score with the patient and his or her family or caretakers. According to the hospital's delirium protocol, high-risk patients (with a score of 5 or more points) received two times daily 1 mg of haloperidol as delirium prevention (in case of absence of contraindications). Independent of the RD score, all patients were monitored for delirium during hospitalization as described above. When patients developed a delirium, they were fully clinically assessed to exclude a somatic cause and treated in collaboration with the psychiatric department.

In 102 patients, the ward nurse at the orthopaedic department performed the RD score a second time when the patient and his or her family arrived on the ward. These 102 patients together with the raters [both ED and ward nurses (doctors)]

were selected randomly. Ward and ED nurses (or doctors) completed the score independent of each other. We used these independently executed RD scores to calculate the interobserver variability. All RD score sheets of all patients were checked for possible errors and, if applicable, were corrected.

Table 1; The Risk Model for Delirium

Predisposing risk factors for delirium	Points
Delirium during previous hospitalisation	5
Dementia	5
Clock-drawing (displaying 10 past 11)	1
- Small mistakes	2
- Big mistakes, unrecognizable or no attempt	
Age	1
- 70 till 85 years	2
- Older than 85 years	
Impaired hearing (patient is not able to hear speech)	1
Impaired vision (vision less than 40%)	1
Problems in activities of daily live	0.5
- Domestic help, or help with meal preparation	0.5
- Help with physical care	
Use of heroin, methadone or morphine	2
Daily consumption of 4 or more alcoholic beverages	2
Total score	

Statistical Analysis

All the items of the questionnaires were imported into IBM SPSS Statistics 19. (IBM Corporation, Somers, USA)

Clinical reliability

The clinical reliability of the RD score was analysed using the intraclass correlation coefficient (ICC) and the kappa coefficient. The ICC and the kappa coefficient are measures of the interobserver reliability, which assesses the degree in which observers assign the same ratings. Values of 0–0.20 were regarded as slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement [25]. As a measure of test–retest agreement, the standard error of measurement was calculated by dividing the mean difference in score between the initial test and the retest by the square root of 2 [26]. The standard error of measurement must be interpreted in relation to the mean. To account for this relationship, the coefficient of variation was calculated. In order to test the validity of the results of this retrospective analysis of the RD score, a

post hoc power analysis was performed. A sample size of 70 subjects with two observations per subject achieved an 84% power to detect an ICC of 0.70 under the alternative hypothesis when the ICC under the null hypothesis is 0.50 using an F-test with a significance level of .05 (calculated with PASS 2008, version 08.05).

Validity

A receiver operating characteristics curve (ROC) was created by plotting the sensitivity (true-positive rate) versus the 1−specificity (false-positive rate). The actual area under the ROC (AUROC) measures the ability of the instrument to classify correctly the patients with and without a high risk for delirium to identify the best cutoff point. The percentages of scores below 5 and above 14 for the RD score were calculated to assess floor and ceiling effects.

Test items statistics

Reliability of the individual items of the RD score was expressed using the ICC of these items. Spearman correlation coefficient was calculated between items of the RD score and the occurrence of delirium to determine the convergent validity. Furthermore, the odds ratio (OR) of each score item for the prevalence of a delirium was calculated using logistic regression analysis with the score items separately as independent variables. To test whether risk factors other than the RD score items would improve the risk model, a multivariable logistic regression was repeated with the RD score dichotomized in high- (score≥4) and low-risk (score<4) patients. The items age, gender, ASA score, fracture type, psychotropic drug use, presence of a partner and institutional residence were used as possible predictors for delirium [27, 28]. Based on the ROC curve analysis, the optimal cutoff point of the RD score was considered to be 4 instead of the clinical cutoff of 5 points. The likelihood ratio backward test was conducted to find the best-fit model by selecting the variables one by one. The probability for entry was set at .05, and the probability for removal at .10.

Feasibility

To assess the clinical feasibility, all the RD score sheets were evaluated for errors in interpreting or skipping items and summation of the individual item scores.

Results

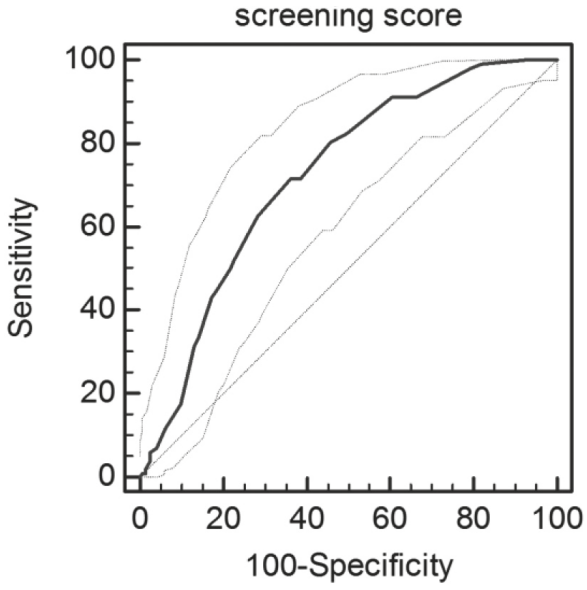
Final analysis was performed in 378 patients; 110 (29.1%) had a partner at admission, 83 (22%) suffered from dementia, 250 (66.1%) lived noninstitutionalized, 252 (66.7%) had an ASA classification of I/II, and 124 (32.8%) used psychotropic drugs. The mean (S.D.) RD score was 4.9 (3.7), 221 (58.5%) patients were classified

as low risk (<5 points), and 157 (41.5%) patients were classified as high risk (≥5 points) based on the clinical cut-off point. Delirium was diagnosed in 102 (27%) patients, 29 (14.1%) in the low-risk and 73 (42.4%) in the high-risk group.

Clinical Reliability In 102 patients (26.9%) an independent nurse executed the RD-score for the second time. The intra-Class Correlation coefficient (ICC) for a single measure was 0.77 (90% CI 0.68-0.84). ICC for an average measure of the two observers was 0.87 (90% CI 0.81-0.91). The standard error of measurement of these 102 duplicate tests was 1.73. The coefficient of variation of the standard error of measurement was 29.4%.

Validity Figure 1 shows the ROC; the AUROC was 0.73 (95% CI 0.68–0.77), and the best cut-off point for balancing sensitivity and specificity was 4 points. This was different from the cut-off point of 5 points that was used in daily practice to define high-risk patients. RD-scores ranged from 0 till 17 points. The RD-score was 5 points or less in 56.6% of all patients (i.e. floor effect), 2.4% of the cohort scored 15 points or more (i.e., no ceiling effect).

Figure 1; ROC curve of the RD-score with 95% confidence intervals. The diagonal indicate results no better than chance.



The ability to predict delirium for both the cut-off point of 4 and 5 is shown in table 2. The likelihood ratio of a screening score ≥4 is 1.86, which means that the probability of a screening score ≥4 being associated with delirium is 1.86 times

more than the probability of this outcome is associated with no delirium. The likelihood ratio of a screening score <4 is 0.33, meaning that the probability of having a screening score <4 and a delirium is 0.33 less than the probability of having a screening score <4 and no delirium.

Table 2; Results of the validity analysis of the Risk Model for Delirium for two cut-off points of the RD-scores

Cutoff point RD-score	**≥4**	**≥5**
Sensitivity % (CI)	80.4% (72.2-88.1)	68.6% (58.6-77.3)
Specificity % (CI)	56.2% (50.1-62.1)	66.3% (60.4-71.8)
Positive Predictivity % (CI)	40.7% (33.9-47.8)	42.9% (35.3-50.9)
Negative Predictivity % (CI)	89.1% (83.2-93.1)	85.1% (79.5-89.5)
Likelihood ratio Positive (Sens/1-Spec)	1.86 (1.6-2.2)	2.04 (1.6-2.5)
Likelihood ratio Negative (1-Sens/Spec)	0.33 (0.2-0.5)	0.47 (0.4-0.6)
Correlation with delirium	0.33	0.31

CI= 90% confidence interval

Test Item statistics

The RD scores of all patients were analysed per item as scored on the form. The prevalence of the following risk factors for a delirium was as follows: a delirium during a previous hospitalization was found in 50 patients (13.2%), 87 patients (23%) suffered from dementia, 89 patients (28.6%) made small mistakes, and 99 patients (33.7%) made big mistakes during clock-drawing. An impaired hearing was scored for in 100 (26.5%) patients, an impaired vision in 66 (17.5%), 214 patients (56.6%) needed help with the preparation of their meals or help for domestic work, and 158 patients (41.8%) received help with physical care. Nine patients (2.4%) had a daily consumption of more than four alcoholic beverages, and only five (1.3%) used heroin, methadone or morphine. The reliability (ICC and kappa) of the items of the RD score is displayed in Table 3. The reliability of dementia was almost perfect: an ICC and kappa of 0.86. The use of heroin, methadone or morphine showed only a slight reliability (ICC and kappa of 0.01). The correlations between delirium and items in the RD score expressed in OR are displayed in Table 2. “Impaired hearing,” “impaired vision,” “use of heroin, methadone or morphine” and “daily consumption of four or more alcoholic beverages” had no significant correlation (both the ICC and OR) with delirium. In the multivariable logistic regression analysis, an RD score of ≥4 (OR 7.1, CI 3.87–13.02, Pb.001), a trochanteric fracture (OR 1.79, CI 1.07–3.01, P=.03) and male gender (OR 1.90, CI 1.06–3.43, P=.03) were significant independent predictors for a delirium.

Table 3 Reliability (ICC and kappa) and ORs of the items of the RD

Risk factor	ICC single	CI	ICC-av#	CI	Kappa	CI	OR	CI	P value
Delirium during previous hospitalization	0.59	0.45-0.70	0.74	0.62-0.83	0.59	0.39–0.79	2.96	1.61-5.45	<0.001
Dementia	0.86	0.80-0.90	0.92	0.89-0.95	0.86	0.74–0.97	2.75	1.66–4.56	<0.001
Clock-drawing	0.72	0.57-0.83	0.84	0.73-0.91	0.72	0.73–0.91			
Small mistakes in clock-drawing	-	-	-	-	-	-	2.27	1.10–4.71	.028
Big mistakes in clock-drawing	-	-	-	-	-	-	3.50	1.77–6.93	<0.001
Age	0.72	0.61-0.80	0.84	0.76-0.89	0.72	0.54–0.89			
70–85 years	-	-	-	-	-	-	4.05	0.92–17.77	.064
Older than 85 years	-	-	-	-	-	-	6.62	1.52–28.87	<0.001
Impaired hearing (patient is not able to hear speech)	0.59	0.45-0.71	0.74	0.62-0.83	0.59	0.42–0.76	1.31	0.79–2.16	.291
Impaired vision (vision less than 40%)	0.49	0.33-0.63	0.66	0.50-0.77	0.49	0.30–0.69	1.12	0.62–2.01	.716
Domestic help or help with meal preparation	0.52	0.36-0.65	0.68	0.53-0.78	0.52	0.34–0.70	2.74	1.66–4.51	<0.001
Help wih physical care	0.51	0.35-0.64	0.67	0.51-0.78	0.50	0.34–0.67	3.46	2.15–5.56	<0.001
Use of heroin, methadone or morphine	0.01	0.0-0.18	0.03	0.0-0.31	−0.01	−0.03 - 0.005	4.15	0.68–25.21	.124
Daily consumption of 4 or more alcoholic beverages	0.66	0.53-0.76	0.79	0.70-0.86	0.66	0.21–1.0	1.36	0.34–5.56	.707

Av.#=average (after repeated measurement).

Table 4: Correlations between delirium and the items of the RD and between the items themselves

	Delirium	delirium during previous hosptalisation	dementia	Clock-drawing	age	impared hearing	impaired vision	domestic help or help with meal preparation	help with physical care	use of heroin, methadone or morphine
Delirium during previous hosptalisation	.185**									
Dementia	.207**	.177**								
Clock-drawing	.215**	.158**	.345**							
Age	.157**	.082	.470**	.231**						
Impaired hearing	.054	-.075	.083	.040	.242**					
Impaired vision	.019	.006	.110*	.107	.120*	.309**				
Domestic help or help with meal preparation	.207**	.153**	.224**	.317**	.230**	.114*	.150**			
Help wih physical care	.270**	.223**	.326**	.343**	.219**	.112*	.161**	.666**		
Use of heroin, methadone or morphine	.086	.023	-.008	.054	-.067	-.069	.069	.101*	.090	
Daily consumption of 4 or more alcoholic beverages	.022	-.061	-.085	-.085	-.069	-.054	.020	.067	-.027	-.018

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed)

Feasibility
In 378 out of 445 patients (84.9%) the RD-score was completed sufficiently. In some of these scores, mistakes were made in interpreting or skipping items and summation of the individual item scores. As a result of this, nine patients were categorized in the wrong group; four should have been qualified as low-risk instead of high-risk and five vice versa.

Interpretation of the form and specific items. In nine patients who lived in a nursing home, no points were assigned for help with meal preparation or domestic help, nor for help with physical care. None of these patients would have shifted to another risk group if corrected. In two patients that suffered from dementia according to the medical records, no points were assigned for this item and in five patients who did receive points for dementia, this diagnosis was not mentioned in their medical records. Correcting for this error would lead to a shift from two patients from low to high-risk and 5 from high- to low-risk. In 22 patients the points for age were not rightfully assigned; 17 patients were appointed too few points, the other five too many. Three of these patients would be treated as high-risk patients instead of low-risk patients, if the age points would be assigned rightfully. One patient would shift to the low- from the high-risk group.

Skipping items. In 84 (22.2%) patients, the clock-drawing part of the RD score was not completed, and no points were assigned to this item. In 47 of the 84 patients, an RD score of more than 5 points was already achieved based on the other items. In eight patients with no points on any other items on the RD score, clock-drawing was not performed; therefore, it was without consequences for shifting to the high-risk group. In the other patients that did not perform the clock-drawing, nine would have shifted to the high-risk group if they made big mistakes in this task.

Summation errors. In six patients errors were made in summation of the points of the individual score items; two patients were treated as low-risk patients while they were actually high-risk patients. In the other four patients, the summation error had no consequence. Three other patients were assigned 1 point for respectively delirium or dementia (instead of 5 points). This had no consequence for the risk group to which they were assigned originally.

Discussion

In this paper, we analyse the validity of the RD score, a valuable new risk model for delirium in hip fracture patients. The RD score showed good reliability and validity.

Furthermore, its clinical feasibility was reasonable, with an acceptable participation rate in daily use. The validity of the RD score was improved by adding the items "male gender" and "type of fracture" and removing the items "daily consumption of more than four alcoholic beverages" and "use of heroin, methadone or morphine."

The RD score had a good interobserver agreement, which improved when a second observer was added. However, in daily practice, the distinction between two groups (i.e., low or high-risk patients) with a single observer will suffice. In this population of hip fracture patients, the RD score had a clear floor effect; thus, it is not very sensitive to detect a delirium risk in patients with a low score (i.e., low risk). An explanation might be that the delirium incidence in our cohort (27%) was too low to differentiate between patients at risk or not at risk for delirium in this low-risk group. Another explanation might be that the current RD score items are not sensitive enough to differentiate for the risk of developing delirium in low-risk patients. The RD score could be improved by adding more relevant risk factors in order to diminish this floor effect, as is discussed below.

As for validity, the RD score had a high sensitivity and a moderate specificity using the optimum cutoff level of 4 points. The AUC was moderate, and the negative predictive value was high; thus, the RD score is suitable as a screening tool for evaluation of the risk for delirium in this patient group. The moderate specificity is of less clinical importance since this high-risk group is probably more closely monitored for delirium in daily practice.

All items of the RD score, as well as potential new items (like gender and type of fracture), were evaluated for their individual effect (i.e., multivariable regression analysis) on the presence of delirium, as was their correlation with each other. The item "dementia" of the RD score showed high correlations with the prevalence of delirium and with the other RD score items and thus severely influenced the RD score. Two items of the RD score could be removed ("use of heroin, methadone or morphine" and "daily consumption of four or more alcoholic beverages"). These two items were only scored positive in a very low number of hip fracture patients and had no significant correlation with the occurrence of a delirium. Two new items ("male gender" and "trochanteric fracture") were added to improve the model. This is in contrast to two meta-analyses on delirium which report no or "a non-convincing" correlation between male gender and presence of delirium [27, 28]. Two other studies did find a negative correlation between male gender and delirium [29, 30]. However, the individual effect of these two items on occurrence

of a delirium was smaller than the compound of a high RD score (i.e., 4 and more points). As for the effect of "fracture type," none of the meta-analyses did include this risk factor [27, 28].

The items of the RD score can easily determined at the ED in an interview with both patients and family or caregivers. Adherence to the RD score protocol was good (85%). Of the 15% of all RD scores which were not completed, clock-drawing was the most frequently noncompleted item. Since painful hip fracture patients are in a supine position on a stretcher and often have an additional injury to the dominant arm, drawing might be difficult. Furthermore, half of the noncompleted clock-drawings were found in patients that already scored into the high-risk group (4 and more points) due to the other RD score risk items. Nevertheless, clock-drawing had a reasonable reliability and correlates with delirium. Therefore, better scoring of this item will be facilitated with the addition of a short manual explaining the necessity to have the clockdrawing performed by each patient.

Several risk models for delirium have previously been published [6–12, 31] However, they contained items that were not applicable to hip fracture patients since they were either specific for a certain patient group [medical ward, (cardio) vascular surgery] or designed for elective admissions. Furthermore, some items of these models take time and skills to obtain, like the APACHE II score or the MMSE used in the model of Kalisvaart [12–14]. The RD score is a relatively simple model that works in daily practice and has now been validated for acute admissions of hip fracture patients.

The prospective study design, large sample size and the use of a predefined risk stratification model are important issues for interpretation of our results. A substantial amount of the RD scores was repeated; thus, reliability could be calculated. However, two limitations remain. The main limitation is the diagnosis of presence of a delirium and mental impairment, this despite the fact that in this study delirium was diagnosed based on the DSM-IV classification [18].We did not use a specific instrument like the Confusion Assessment Method to establish delirium [32]. Furthermore, presence of dementia was based on history taking; a cognitive impairment score like the MMSE was not used [14] .High-risk patients were treated with prophylactic low dose haloperidol. A recent Cochrane review, a randomized controlled trial of Kalisvaart et al. and our clinical series demonstrated that haloperidol did not have a diminishing effect on delirium incidence [5, 15, 33]. Therefore, prophylactic haloperidol most probably did not influence the results of

the present study. However, labelling patients as "high-risk" might bias the nursing staff; they might be triggered to observe patients more closely for presence of a delirium. Discarding patients because of an incomplete RD score could potentially have influenced our outcome. However, this is highly unlikely since the incidence of delirium and the age of these patients were comparable to the evaluated cohort. Finally, we decided to correct errors in summation and errors as a consequence of not assigning the right amount of points to a specific item. This was only necessary in a limited number of cases, which emphasizes the clinical usefulness of the RD score.

The RD score is a recently introduced score that determines the risk for a delirium in hip fracture patients. It has a reasonable clinical feasibility and a good reliability and validity. It would be of additional value to adjust the model by adding "male gender" and 'trochanteric fracture' and removing "daily consumption of more than four alcoholic beverages" and "use of heroin, methadone or morphine" as score items.

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CHAPTER 7

FACTORS ASSOCIATED WITH THE COURSE OF HEALTH-RELATED QUALITY OF LIFE AFTER A HIP FRACTURE

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Abstract

Introduction

The number of hip fracture patients is expected to grow the forthcoming decades. Knowledge of the impact of the fracture on the lives of elderly could help us target our care. The aim of the study is to describe HRQoL (Health Related Quality of Life) after a hip fracture and to identify factors associated with the course of HRQoL in the first postoperative year.

Methods

335 surgically treated hip fracture patients (mean age 79.4 years, SD 10.7, 68 % female) were included in a prospective observational cohort. HRQoL was measured with the SF-12 Health Survey, composed of the Physical and a Mental Component Summary Score (PCS, MCS) at admission (baseline) and at three and 12 months postoperatively. Eleven predefined factors known to be associated with the course of HRQoL were recorded: age, gender, physical status, having a partner at admission, living in an institution, pre-fracture level of mobility, anemia, type of fracture and treatment, delirium during hospital stay and length of stay.

Results

HRQoL declined between baseline and three months, and recovered between three and 12 months. PCS HRQoL did not recover to baseline values, MCS HRQoL did. Age younger than 80 years, ASA classification I and II, higher prefracture level of mobility, intracapsular fracture and treatment with osteosynthesis (compared to arthroplasty) were associated with greater initial decline in PCS HRQoL, none of the recorded factors were significant for decline in MCS HRQoL.

Conclusion

Both PCS and MCS HRQoL declined after a hip fracture and PCS did not recover to baseline values. Healthier patients may need extra care to prevent them from having a steep decline in postoperative PCS HRQoL and arthroplasty should be considered with low threshold.

Introduction

The number of hip fracture patients will keep growing, with an estimated increase in Europe form 615.000 in 2010 to 815.000 in 2025 (+32%) due to demographic changes. [1] Hip fracture patients suffer from a decline in mobility [2, 3] and loss of independence [4, 5] in the first year after the fracture treatment. The large and increasing number of hip fracture patients in combination with the large impact on patients' daily living activities stresses the importance of analysis of factors associated with postoperative outcome in these patients.

Previous studies have shown that the Health-Related Quality of Life (HRQoL) score decreases after a hip fracture, whereas the Physical health Component Summary Score (PCS) decreases more than Mental health Component Summary Score (MCS). [6–14] Older age, more co-morbidities [12], higher baseline HRQoL [15, 16], lower body mass index, lower bone mineral density [17] treatment with osteosynthesis [18] and complications after internal fixation of femoral neck fractures [11] were identified as specific risk factors for lower HRQoL after a hip fracture. It has been described earlier that the lowest HRQoL is reached in the first three months after a hip fracture, with some improvement in the years thereafter, however the pre fracture HRQoL is never regained. [19].

The aim of the current study was to evaluate the course of HRQoL with specific emphasis on the risk factors for decline in HRQoL during the first 3 months after a hip fracture and the factors associated with recovery of HRQoL after these 3 months in a large prospective cohort of patients.

Methods

Patient cohort

A prospective observational cohort including 461 hip fracture patients (OTA classification 31-A, B and 32-(1-3).1) [20] aged 50 years and older was conducted. All patients were consecutively admitted to a 450-bed teaching hospital (Delft, the Netherlands) between March 2008 and December 2009. Patients with a fracture due to a high-energy trauma or with a pathologic fracture were excluded. Patients with a contra lateral hip fracture within the time window of the study (n=20), those who were treated conservatively (n=14) and patients who were cognitively impaired (n=92) were excluded from the study. The latter was done because cognitive impairment influences HRQoL questionnaire accuracy. [21] Cognitive impairment was defined as dementia, based upon history taking from patients, family and other caretakers or a delirium at the time of admission (based on the

DSM-IV criteria) [22]. Thus, 335 patients were eligible for the analysis. Length of follow-up for all patients was 12 months or up to death.

Uniform collection and recording of data of all patients of this cohort was achieved by evaluation at admission (baseline) and after three and 12 months, according to the local standardized care pathway for hip fracture patients. [23] Collected demographic data were age (divided in two categories based on the median, younger than 80 years and older than 80 years), gender, American Society of Anesthesiologists (ASA) Physical Status classification [24], presence of a partner at admission, living institutionalized or living at home prior to admission and prefracture level of mobility (mobile with or without an aid). A cane, crutch(es) or walker were all considered an aid. Characteristics obtained during admission were; presence of anemia at admission, defined as a hemoglobin (Hb) below 7.5 mmol/L (12 g/dL) in women and below 8.1 mmol/L (13 g/dL) in men [25], type of hip fracture (intracapsular or extracapsular), type of treatment (osteosynthesis or arthroplasty), diagnosis of delirium based on DSM IV-criteria and length of stay (LOS, divided in two categories based on the median, ≤ or > nine days). Mortality was scored meticulously by repeated consultation of the population registers of the counties in the region of the hospital as well as the hospital's patient registration systems for the full length of follow-up.

Health Related Quality of life (SF-12)

To measure HRQoL, the Dutch version of the SF-12 was used. [26–28] The SF-12 is a twelve-item generic health instrument that evaluates eight domains including restrictions or limitations on physical and social activities, normal activities and responsibilities of daily living, pain, mental health and wellbeing and perceptions of health. The SF-12 is divided in a Physical Component summary Score (PCS) and a Mental Component summary Score (MCS), with a maximum score of 100 each. The SF-12 has been shown to be valid, reliable, and responsive in a wide variety of populations and contexts, including patients with orthopaedic conditions [29]. Baseline HRQoL was registered at admission on the Emergency Department. Patients were asked to score their prefracture level of HRQoL retrospective, referring to a period prior to the fracture. Measurement of the HRQoL was repeated prospective during routine follow-up at three and 12 months after the hip fracture in the outpatient clinic or by a questionnaire sent to the patient.

Statistical analysis

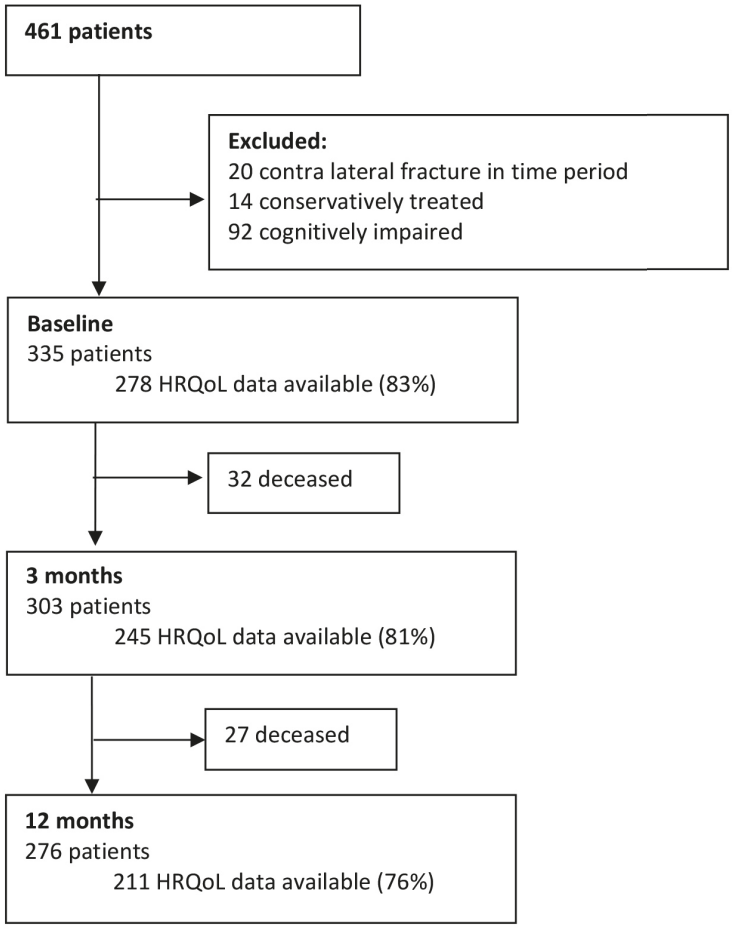
Statistical analysis was performed using SPSS 19.0. (IBM Corporation, Somers, NY, USA) Baseline differences in HRQoL for different patient characteristics (i.e. age, gender) were tested using the unpaired T-test when the data were normally distributed. Decline in HRQoL between baseline and three months was calculated for all patients and for different patient characteristics, an unpaired T-test was used to test for differences.

For all patients with HRQoL data at baseline and at three months a multivariable logistic regression analysis was performed using age, gender, ASA classification, presence of partner at admission, living institutionalized prior to admission, prefracture level of mobility, presence of anemia, type of fracture, type of treatment, occurrence of a delirium and LOS as potential variables associated with decline and recovery of HRQoL. The same analysis was performed for patients with HRQoL data at three months and 12 months. Multicollinearity was tested by Collinearity Statistics. Non-significant variables were removed one by one, removing the largest P-value first, until all remaining variables in the model had a P-value <0.10. The coefficient of determination (R^2) indicating how much of the variability in the PCS and MCS is explained by the explanatory variables, was calculated.

Results

Baseline HRQoL data was complete in 278 patients out of the 335 patients included the cohort (83%), after three months HRQoL data was complete in 245 out of 303 patients (81%). Thirty-two patients (10%) died in the first three months. After 12 months HRQoL was completed in 211 out of 276 patients (76%) (Figure 1). Fifty-nine patients (17.6%) died within the first year after hip fracture at a median of 71.0 days (SD 96 days, interquartile range 22-201). A total of 173 patients (52%) completed HRQoL data at baseline, three months and 12 months. There were 103 patients alive at 12 months who had missing HRQoL data on one or more time points. The patients with complete follow up were more often ASA I/II (n= 140 (81%) versus n= 68 (64%) p=0.005) had more often a partner at admission (n= 83 (52.0%) versus n= 34 (28.9%) p= 0.04) and lived less often in an institution (n= 15 (8.7%) vs. n= 25 (24.5%) p< 0.001). The other characteristics were not different between these groups.

Figure 1; flowcharts of availaible and analyzed patients



Baseline HRQoL PCS and MCS

Table 1 displays baseline characteristics of the cohort. Table 2 displays baseline HRQoL stratified by risk factors. PCS was higher at baseline in the patients younger than 80 years of age, males, patients with ASA classification I/II, with a partner at admission, not living in an institution prior to admission, who were mobile without an aid, who had no anemia at admission and who stayed in hospital shorter than nine days. The baseline MCS was higher for patients younger than 80 years of age, males, patients with ASA classification I/II, with partner at admission, not living institutionalized prior to their fracture, mobile without an aid and who did not suffer from a delirium during admission.

Table 1: baseline patient characteristics

		Number (percentage)
Age (median, range)		median 80.5 (50 - 101)
Gender	Female	227 (68%)
ASA classification	I/II	233 (70%)
Partner at admission [a]	Yes	127 (39%)
Living in an institution prior to admission [b]	Yes	64 (19%)
Prefracture level of mobility [c]	With aid	139 (47%)
Anemia at admission [d]	Yes	124 (37%)
Type of fracture	Intracapsular #	202 (60%)
Type of treatment [c]	Arthroplasty ##	121 (37%)
Delirium [e]	Yes	49 (15%)
Length of stay (median, range)		median 9 (3 – 71)

Values missing [a] = 11, [b] = 1, [c] = 40, [d] = 9, [e]= 4
opposed to Extracapsular
opposed to Osteosynthesis

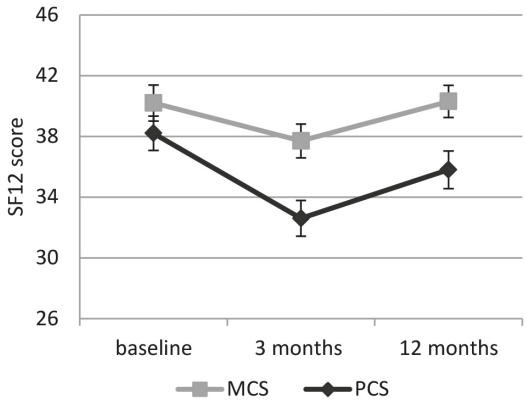
Table 2: baseline physical (PCS) and mental component score (MCS) stratified by risk factors

		PCS	95% CI	P	MCS	95% CI	
All patients (n= 335)		38.2	37.1-39.4		40.2	39.1-41.2	
Age	<80	41.6	40.0-43.1		41.7	40.2-43.2	
	≥80	35.3	33.8-36.7	<0.01	38.8	37.3-40.2	<0.01
Gender	Female	36.9	35.5-38.2		39.8	38.5-41.0	
	Male	41.2	39.2-43.2	0.04	41.0	39.1-42.9	0.04
ASA classification	I/II	40.8	39.6-42.1		41.5	40.2-42.7	
	III/IV	31.5	29.5-33.5	<0.01	36.8	34.9-38.8	<0.01
Partner at admission	Yes	40.7	38.9-42.4		43.0	41.3-44.7	
	No	37.0	35.5-38.5	0.01	38.7	37.3-40.1	0.03
Living in an institution prior to admission	Yes	31.0	28.4-33.7		34.6	32.0-37.1	
	No	39.7	38.5-40.9	<0.01	41.3	40.2-42.4	<0.01
Prefracture level of mobility	With aid	32.4	30.9-33.9		38.1	36.5-39.7	
	Without aid	45.0	43.6-46.4	<0.01	42.8	41.4-44.3	<0.01
Anemia at admission	Yes	35.4	33.5-37.2		39.8	38.0-41.6	
	No	39.9	38.6-41.3	0.05	40.4	39.1-41.8	0.71
Type of fracture	Intracapsular	39.2	37.8-40.7		40.8	39.4-42.2	
	Extracapsular	36.2	34.3-38.1	0.18	39.0	37.1-40.8	0.3
Type of treatment	Arthroplasty	36.8	34.9-38.6		39.2	37.4-40.9	
	Osteosynthesis	39.4	37.9-40.8	0.42	40.8	39.4-42.1	0.25
Delirium	Yes	34.0	31.0-36.9		35.6	32.9-38.4	
	no	39.1	37.9-40.3	0.18	41.0	39.9-42.1	<0.01
Length of stay	< /=9 days	41.6	40.1-43.2		41.6	40.1-43.1	
	> 9 days	35.2	33.7-36.7	<0.01	38.9	37.5-40.3	<0.01

Course of HRQoL

Both PCS and MCS declined in the first three months. (figure 2) PCS did not recover to the baseline value at 12 months follow-up, whereas MCS did.

Figure 2; Course of Mental Component Score (MCS) and Physical Component Score (PCS) in time mean (SD)



HRQoL = Health Related Quality of Live

Factors associated with decline and recovery of PCS

Analysis of difference in HRQoL between baseline and three months shows that male gender, lower ASA classification and higher prefracture mobility level was associated with a higher decline of PCS (univariate analysis, table 3). Higher prefracture mobility level was associated with a higher recovery of PCS between three and 12 months. In multilevel analysis younger age, lower ASA classification, higher prefracture mobility level, intracapsular fracture and treatment with osteosynthesis were independently associated with larger loss in PCS HRQoL in the first three months (table 4). Higher prefracture mobility level, intracapsular fracture, treatment with osteosynthesis and length of stay more than nine days were associated with higher recovery of PCS HRQoL between three and 12 months (table 5). Figure 3 shows PCS course in time stratified by age, ASA, mobility, type of fracture, type of treatment and length of stay.

Table 3; Decline and recovery of the physical component score (PCS) stratified by risk factors

		Decline between baseline and three months			Recovery between 3 and 12 months		
		Δ	CI	P	Δ	CI	P
All patients (n= 218)		-5.6	-6.8; -4.4		3.1	1.8; 4.4	
Age	<80	-6.6	-8.8; -4.3		4.2	1.9; 6.5	
	≥ 80	-4.7	-6.9; -2.5	0.30	2.0	-0.4; 4.3	0.07
Gender	Female	-4.7	-6.7; -2.8		2.4	0.4; 4.5	
	Male	-7.4	-10.2 -4.5	<0.01	4.5	1.5; 7.4	0.12
ASA classification	I/II	-6.9	-8.7; -5.1		3.7	1.8; 5.6	
	III/IV	-1.6	-4.6; 1.4	<0.001	0.9	-2.4; 4.3	0.08
Partner at admission	Yes	-6.0	-8.5; -3.5		4.2	1.6; 6.7	
	No	-5.4	-7.6; -3.3	0.61	2.1	-0.2; 4.4	0.10
Living in an institution prior to admission	Yes	-3.2	-7.2; 0.9		0.9	-3.9; 5.7	
	No	-6.0	-7.7; -4.3	0.15	3.3	1.5; 5.1	0.29
Prefracture level of mobility	With aid	-2.5	-4.6; -0.3		0.6	-1.8; 3.0	
	Without aid	-8.8	-10.7; -6.8	<0.001	5.2	3.1; 7.3	<0.001
Anemia at admission	Yes	-4.0	-6.7; -1.2		2.2	-0.8; 5.2	
	No	-6.5	-8.5; -4.5	0.08	3.5	1.5; 5.6	0.28
Type of fracture	Intracapsular	-6.1	-8.2; -4.1		3.9	1.7; 6.0	
	Extracapsular	-4.8	-7.7; -2.0	0.36	2.2	-0.7; 5.2	0.20
Type of treatment	Arthroplasty	-4,6	-7.3; -2.0		1.4	-1.5; 4.3	
	Osteosynthesis	-6.2	-8.3;-4.2	0.26	3.9	1.8; 6.1	0.06
Delirium	Yes	-3.5	-8.0; 1.1		0.3	-4.7; 5.4	
	No	-6.0	-7.8; -4.3	0.23	3.6	1.7; 5.4	0.14
Length of stay	< =9 days	-6.3	-8.0; -4.5		2.9	1.2; 4.5	
	> 9 days	-5.6	-7.7; -3.5	0.94	3.3	1.5; 5.2	0.78

Table 4 Multivariable analysis of decline in Physical Component Score (PCS) between baseline and 3 months

		B	95% CI	P
Age	<80 years	-4.36	-8.11; -0.60	0.023
ASA classification	I/II	-4.48	-8.28; -0.68	0.007
Prefracture level of mobility	Without aid	-6.15	-9.81; -2.48	0.001
Type of fracture	Intracapsular	-7.48	-12.98; -1.98	0.008
Type of treatment	Osteosynthesis	-7.40	-12.89; -1.92	0.009

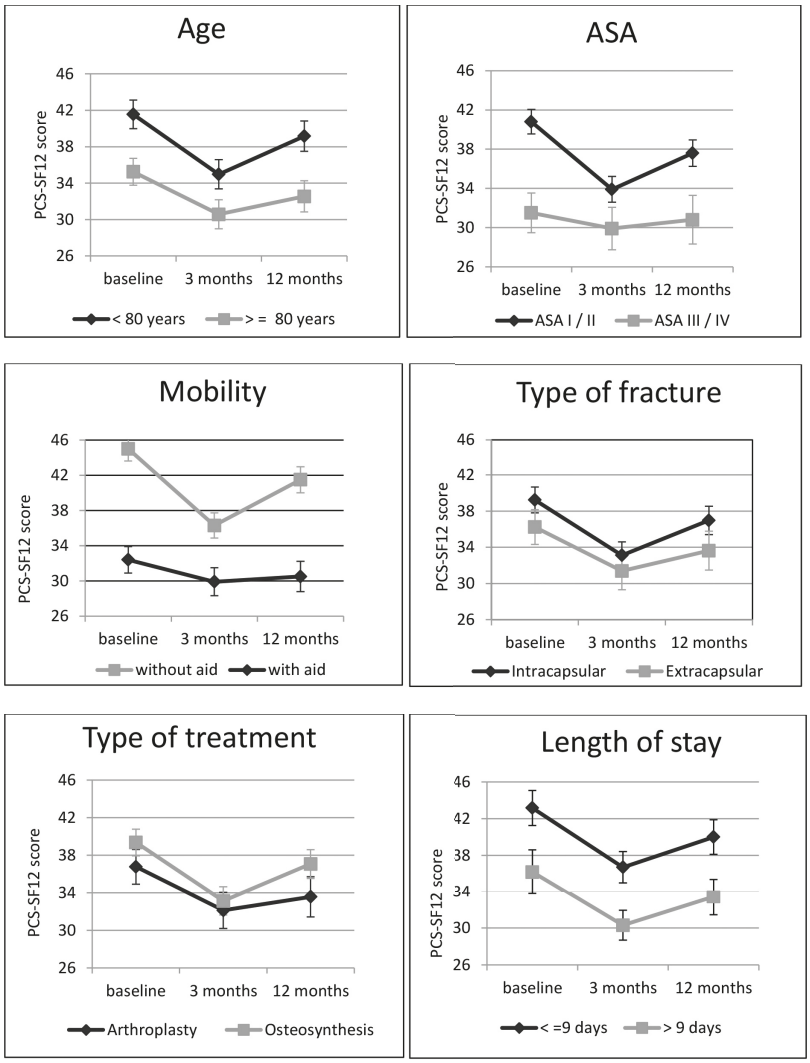
R square = 0.193

Table 5 Multivariable analysis of recovery in Physical Component Score (PCS) between 3 and 12 months

		B	95% CI	P
Prefracture level of mobility	Without aid	3.95	1.33; 6.56	0.003
Type of fracture	Intracapsular	4.36	1.28; 7.43	0.006
Type of treatment	Osteosynthesis	5.49	2.28; 8.70	0.001
Length of stay	> 9 days	3.28	0.64; 5.92	0.015

R square = 0.151

Figure 3; Physical Component Score (PCS) course in time stratified by age, ASA, mobility, type of fracture, type of treatment and length of stay. Mean (SD)



Factors associated with decline and recovery of MCS
Univariate analysis shows none of the studied factors associated with a higher initial decline and a later increase of MCS. No model could be made for MCS decline between baseline and three months and recovery between three and 12 months, as none of the risk factors were significant predictors in the multilevel analysis.

Discussion

In this observational cohort study on HRQoL in hip fracture patients during the first postoperative year, HRQoL declined, which was more pronounced in the PCS than in the MCS. The PCS did not recover to baseline values at 12 months postoperative, whereas MCS did. Age, ASA classification, prefracture level of mobility, type of fracture and type of treatment were associated with the decline in the PCS.

Our findings that patients did not recover to their baseline PCS level, but did recover to their preoperative MCS level is in accordance with other cohort studies. [6, 9, 10, 12–14, 17, 19, 30, 31] A meta-analysis by Peasgood et al (2009) [19] also showed the lowest HRQoL in the first three months after a hip fracture, with some improvement in the years thereafter, but never full recovery to the prefracture level.

Lower ASA classification, higher prefracture level of mobility and younger age were associated with a relatively larger decline in PCS HRQoL after a hip fracture: i.e. the more healthy patients suffered the most from the sequelae of a hip fracture. An international cohort study on 1,273 hip fracture patients showed that patients with higher HRQoL at baseline had greater loss of HRQoL after their hip fracture.[15] A study on the same cohort of hip fracture patients as the current study focussing on of the level of mobility showed that the most mobile patients were least likely to return to their pre fracture mobility level after three months. [2] Since these healthier and more active patients have a larger decline of their PCS HRQoL, more attention in the postoperative rehabilitation should be given to them, whilst a general feeling might exist, that these healthier patients might need less attention. Special rehabilitation programs with focus on mobilization and early discharge policy for this group could contribute to this. Younger age in our cohort was associated with a larger decline in the first three months, while most studies showed that older age is associated with larger loss in HRQoL. [12, 15] These other studies however measured HRQoL after one or two years, and younger patients recover quicker after these first three months. Patients with intra capsular fractures are in general younger (mean two years), more mobile and

less dependent regarding activities of daily living compared to patients with extra capsular fractures. [32–34] Since these patients with an intra capsular fracture seems to be healthier, they are more likely to have a larger initial decline in HRQoL.

In the Norwegian hip fracture register, patients treated with an osteosynthesis for a displaced femoral neck fracture had higher reoperation rates, higher long-term mortality and a lower HRQoL after four months, compared to those treated with a hemi arthroplasty. [18] Buecking et al. demonstrated that treatment with osteosynthesis was associated independently with a larger decrease in HRQoL at discharge.[35] Both studies confirm our finding that patients treated with osteosynthesis have a larger loss in HRQoL compared to those treated with arthroplasty. This suggests that arthroplasty should be considered with a low threshold. However in our study osteosynthesis was associated with a larger recovery in HRQoL between three months and one year. This resulted in an equal loss in HRQoL between osteosynthesis and prosthesis in the first year.

None of the factors were significant predictors for decline or recovery of MCS HRQoL after a hip fracture. This is in contrast to others who found that comorbidities were associated with a larger decline in MCS HRQoL, but that study included only 61 patients. [12]

The strengths of our study are its prospective character, the size of the cohort (n=335) and the length of follow up (one year). Only a few prospective studies reporting on factors associated with the course of PCS HRQoL after a hip fracture are known [12, 15, 35] Two studies had a relatively short follow-up: one (n=402) up until discharge, [35] the other (n=1273) four months. [15] The study with the longest follow-up (two years) was small study (n=61). [12]

A limitation of our study is the incomplete follow-up: the follow-up rate ranged from 76 to 83%, corrected for mortality. This follow-up rate can be classified as substantial. The mortality rate of 17.6% is lower than the recently reported average 1-year mortality after hip fracture of 22 to 29%. [36] Since we used multilevel analysis, a part of the problem of the incomplete follow-up is addressed for in our data analysis. Inclusion of the pre-operative and three months results of patients who died in the first year after the fracture might have influenced our results, while those patients probably had lower HRQoL scores when they would have been alive at 12 months. Recall bias may be present for baseline HRQoL, which was recorded at admission in the hospital in the emergency department,

but recent literature showed that recall data is accurate. [37–39] Also since we excluded cognitive impaired patients, our results can be generalizable only to hip fracture patients who are mentally fit. [21] Medical comorbidities were not scored as individual parameter, but ASA score was used as a reflexion of comorbidities. Finally, the SF-12 was used to measure HRQoL although in 2007 the European Consumer Safety Association advised to use a combination of EuroQol-5D and Health Utilities Mark III in all studies on injury-related disability [40]. However, the SF-12 has been shown to be valid, reliable, and responsive in a patients with orthopaedic conditions [29].

In summary, the initial decline in PCS HRQoL, three months after a hip fracture, was larger in healthier patients (younger than 80 years, higher pre fracture level of mobility, ASA I and II et cetera), most probably due to their higher prefracture values. This implies that these patients need extra care or health professionals should be aware that also "healthy" patients could deteriorate after a significant life event like a hip fracture. Thus prevention from overall decline in HRQol should also be focused at this patient group and not only on the frail patient group. Special rehabilitation programs and discharge policy for this group and not only for the more frail patients is justified. Since the decline in PCS HRQoL in the first three months was larger in patients treated with osteosynthesis compared to those treated with arthroplasty of the hip, the latter option should be considered with a low threshold.

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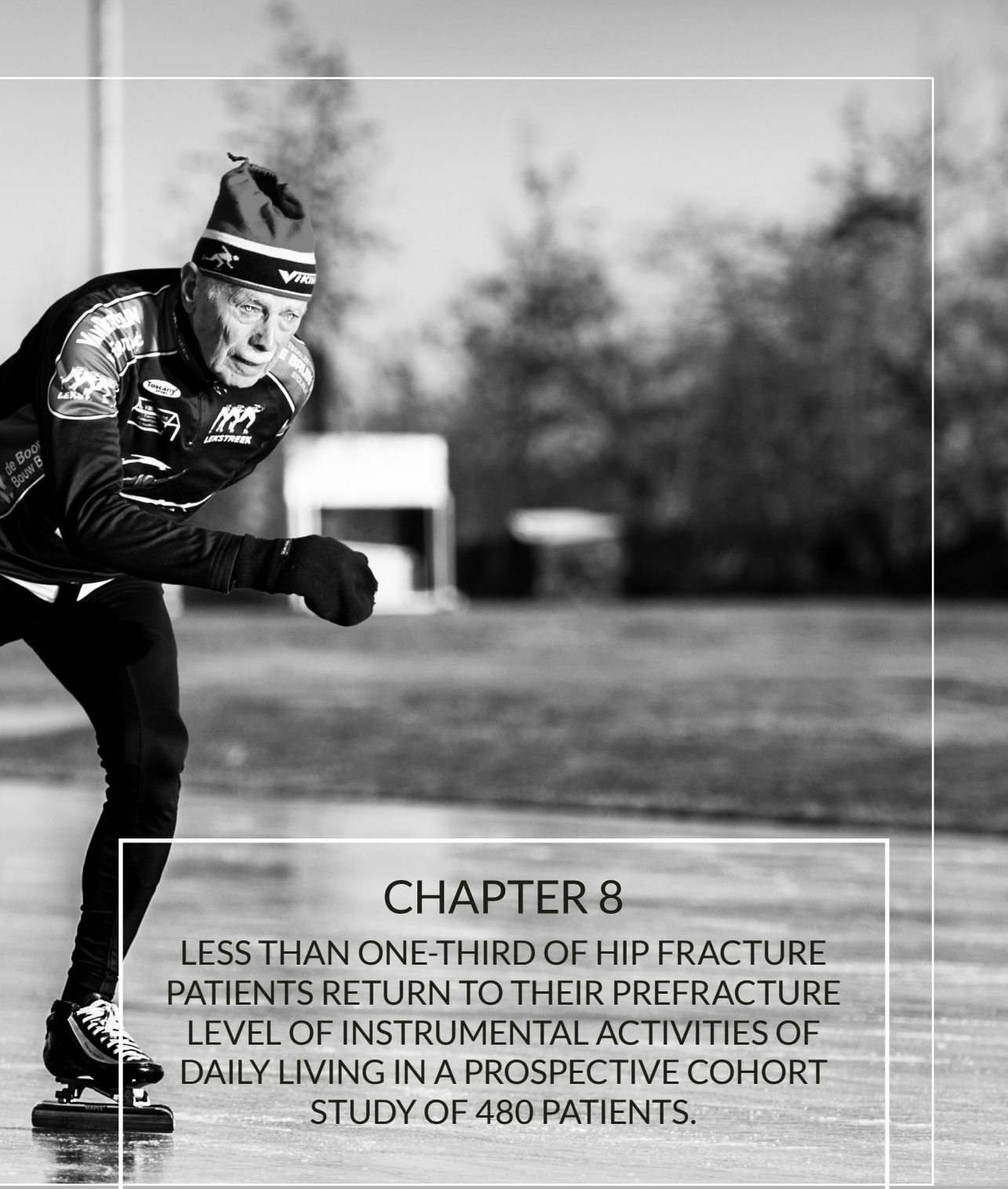

CHAPTER 8

LESS THAN ONE-THIRD OF HIP FRACTURE PATIENTS RETURN TO THEIR PREFRACTURE LEVEL OF INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN A PROSPECTIVE COHORT STUDY OF 480 PATIENTS.

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Abstract

Introduction

A significant loss of instrumental activities of daily living ((i)ADL) after a hip fracture has been reported. The aim of the present study was to identify specific predictors for low (i)ADL after a hip fracture, in order to target better postoperative care for these patients.

Methods

A prospective observational cohort study of 480 hip fracture patients was performed. (i)ADL was measured at baseline and after three and 12 months using the Groningen Activity Restriction Scale (GARS). Multivariable logistic regression analysis was performed using age, gender, American Society of Anesthesiologists (ASA) classification, prefracture living with a partner, prefracture living situation, prefracture use of walking aids, type of fracture, type of anaesthesia, length of hospital stay, postoperative complications and prefracture (i)ADL as potential predictors for low (i)ADL after a hip fracture. Correlation between (i)ADL, mobility and living situation both at admission and three and 12 months postoperatively were measured.

Results

Three months after hip fracture treatment, 24% of patients returned to their baseline (i)ADL level, at 12 months postoperative this was 29%. Factors associated with a larger loss in (i)ADL after a hip fracture were higher age, prefracture living with a partner, prefracture living at home, prefracture use of walking aids and longer length of hospital stay. Correlation between (i)ADL and living situation was 0.69, between (i)ADL and use of walking aids 0.80.

Conclusion

Return to prefracture (i)ADL level was low. Healthier patients have a steeper decline in postoperative (i)ADL.

Introduction

It is expected that in 2050 the annual number of hip fracture patients will increase to one million fractures in the USA and 4.5 million fractures worldwide. [1, 2] A hip fracture often leads to a functional decline and loss of mobility. [3] Even more, functional decline is associated with disability, institutionalization and even death of the patient. [4] Nevertheless, a functional decline partially recovers during the first six months after the hip fracture. [3] According to a recent review 34 to 59% of all hip fracture patients regain their basic Activities of Daily Living (ADL) by three months and 42 to 71% by six months. [3]

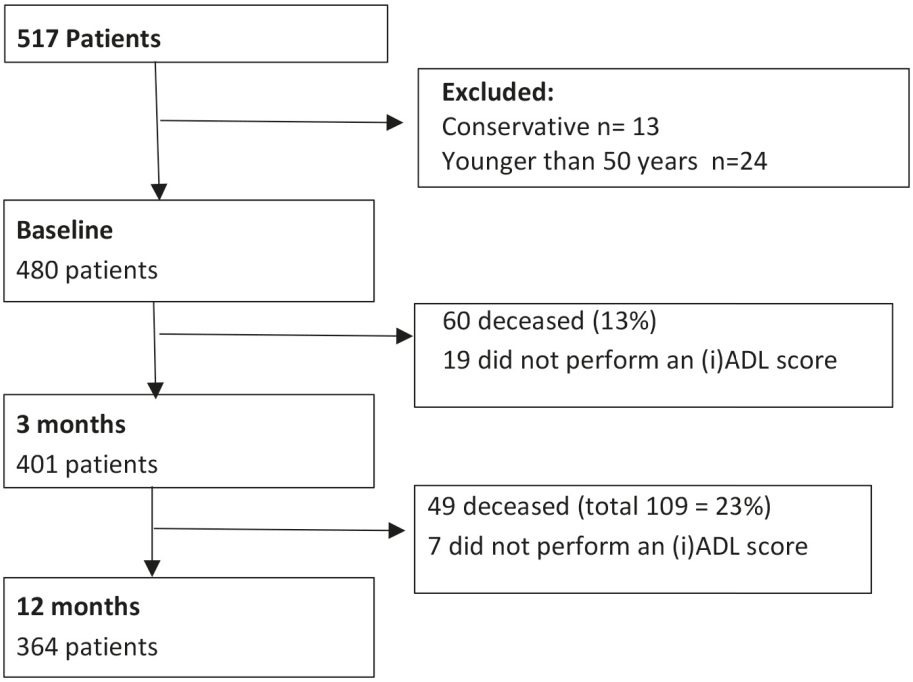
Functional decline can lead to a lower Quality of Life for the patients [5] and higher costs for society (as of more institutionalized care or domestic help). [6] It is known that function after an hip fracture can be improved by a number of interventions like home- based rehabilitation [7] anabolic steroids [8] and comprehensive geriatric care [9]. However, these measures have to be targeted on the populations that needs it the most while they are expensive. Therefore, it is important to identify risk factors for a larger functional decline. Age, the number of comorbidities, cognitive status and prefracture functional level are associated to some extent with this functional decline and recovery after hip fracture surgery [10–12] however the exact predictors for functional decline are at this moment unknown. Knowing these predictors for functional decline can make our care more "tailor made" and using these interventions in patients at risk for larger decrease in ADL could potentially lead to better outcome and saving of costs by reducing the need for help in ADL. Therefore the aim of the current study was to evaluate the functional decline during the first year after a hip fracture and to identify potential predictors for larger loss in (instrumental)ADL in a prospective cohort study.

Methods

The data of patients of the current study were retrieved from our prospective observational cohort of 517 hip fracture patients. The study did not fall under the scope of the medical research with human subjects act (WMO), therefore no ethical approval was necessary. Information of this observation study for patients or family members was provided in a binder specially designed for hip fracture patients in our hospital. [13] All hip fracture patients were consecutively admitted to a 450-bed teaching hospital (Delft, the Netherlands) between January 2008 and December 2009. Patients with a fracture due to a high-energy trauma or with a pathologic fracture were not included in this database. All patients had a complete data set of baseline functional status. Patients younger than 50 years (n=24) and those treated

conservatively (n=13) were excluded from the database for this specific study as is shown in the flowchart. Length of follow-up for all patients was at least 12 months or until death occurred. The number of patients at baseline, three and 12 months are described in the flowchart. (figure 1)

Figure 1. flowchart of included and excluded patients



Uniform collection and recording of data of all patients of this cohort was achieved by evaluation at admission (baseline) and after three and 12 months, according to the local standardized care pathway for hip fracture patients. [13] Collected demographic data were age, gender, American Society of Anesthesiologists (ASA) Physical Status classification [14] prefracture living with a partner, prefracture living institutionalized or living at home and prefracture use of walking aids. A cane, crutch(es) or walker were all considered an aid. Characteristics obtained during admission were; type of hip fracture (intracapsular or extracapsular), type of treatment (osteosynthesis or arthroplasty), type of anesthesia (locoregional or general) and length of hospital stay. Complications were scored during hospital stay. Mortality was scored meticulously by repeated consultation of the population

registers of the counties in the region of the hospital as well as the hospital's patient registration systems for the full length of follow-up.

(i)ADL

Daily life functioning can be divided in two categories, Activities of Daily Living (ADL) and instrumental Activities of Daily Living (iADL). ADL are self-care activities (like dressing) while iADL are activities necessary for independently living in a community (shopping, preparing meals). We measured both ADL and iADL in one questionnaire using the Groningen Activity Restriction Scale (GARS). [15] The GARS consists of 18 questions 11 ADL items and seven iADL items. The questionnaire is displayed. (figure 2) The score ranges therefore from 18 to 72. With a score of 18 one can perform all the activities without any difficulty; with a score of 72 one cannot perform any activity without the help of others. Reliability of GARS is acceptable, with good to excellent internal consistency (Cronbach's alpha 0.86-0.94), poor to acceptable test- retest correlation (0.53-0.74) and acceptable inter-item correlation (0.25 to 0.54). Construct validity is good (Pearsons correlation coefficient; 0.65 with "physical functioning" in the SF-36) [15, 16] However responsiveness, the minimal clinically important difference (MCID) and ceiling and floor effect are not well known. Baseline (i)ADL was registered at admission on the Emergency Department. Patients were asked to score their prefracture level of (i)ADL retrospective, referring to a period prior to the fracture. Measurement of the (i)ADL was repeated prospective during routine follow-up at three and 12 months after the hip fracture in the outpatient clinic or by a questionnaire sent to the patient. In order to measure whether a lower level of (i)ADL is correlated to lower mobility and dependent living situation after a hip fracture, the percentage of patients mobilizing with aid and the percentage of patients living institutionalized were measured at baseline and three and 12 months after the fracture.

Figure 2. GARS questionnaire

Activities of daily living (ADL)

1. Can you, fully independently, dress yourself?
2. Can you, fully independently, get in and out of bed?
3. Can you, fully independently, stand up from sitting in a chair?
4. Can you, fully independently, wash your face and hands?
5. Can you, fully independently, wash and dry your whole body?
6. Can you, fully independently, get on and off the toilet?
7. Can you, fully independently, feed yourself?
8. Can you, fully independently, get around in the house (if necessary, with a cane)?
9. Can you, fully independently, go up and down the stairs?
10. Can you, fully independently, walk outdoors (if necessary, with a cane)?
11. Can you, fully independently, take care of your feet and toenails?

Instrumental activities of daily living (IADL)

12. Can you, fully independently, prepare breakfast or lunch?
13. Can you, fully independently, prepare dinner?
14. Can you, fully independently, do "light" household activities (for example, dusting and tidying up)?
15. Can you, fully independently, do "heavy" household activities (for example, mopping, cleaning the windows, and vacuuming)?
16. Can you, fully independently, wash and iron your clothes?
17. Can you, fully independently, make the beds?
18. Can you, fully independently, do the shopping?

It has a four-category response format:

1- able to perform the activity without any difficulty;
2- able to perform the activity with some difficulty;
3- able to perform the activity with much difficulty;
4- unable to perform the activity independently.

Statistical analysis

Statistical analysis was performed using SPSS 19.0. (IBM Corporation, Somers, NY, USA) (i)ADL was not normally distributed. Difference in (i)ADL between baseline and three months was calculated with an Wilcoxon signed rank test. A multivariable logistic regression analysis was performed to calculate factors associated with baseline (i)ADL. Age, gender, ASA classification, prefracture living with a partner, prefracture living situation, prefracture walking with aids and type of fracture

were used as potential variables associated with baseline (i)ADL. To determine factors associated with (i)ADL at three and 12 months type of anaesthesia, length of hospital stay, postoperative complications and prefracture (i)ADL were added to the same analysis. Furthermore predictors for decline in (i)ADL and later recovery in (i)ADL were calculated with a multivariable logistic regression analysis with the same potential variables. Multicollinearity was tested by Collinearity Statistics. Non-significant variables were removed one by one, removing the largest P value first, until all remaining variables in the model had a P value ≤ 0.10. The coefficient of determination (R^2) indicating how much of the variability in the (i)ADL is explained by the explanatory variables was calculated.

Correlations between (i)ADL, percentage of patients walking with aid and percentage of patients with an independent living situation were calculated with Pearson correlation. 0–0.20 was regarded as slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement [17]

Results

480 patients were included in the study. Median age was 83 years, 71% was female. Baseline characteristics are displayed in table 1. Mortality was 13% at three months (n=60) and 23% at one year (n=109).

Table 1. Baseline characteristics

Characteristic		Number (%)
Age (median, range)	Years	Median 82.6 (range 50-101)
Gender	Female	342 (71%)
ASA classification	ASA I and II	328 (68%)
Prefracture living with a partner *	Yes	158 (33%)
Prefracture living situation	Independent	324 (68%)
Prefracture use of walking aids	No aid	190 (40%)
Type of Fracture	Intracapsular	284 (59%)
Type of Treatment	Osteosynthesis	294 (61%)
Type of anesthesia	Locoregional	450 (94%)
Length of hospital stay (median, range)	Days	Median 10 (range 2-71)
Postoperative complications	One or more	248 (52%)

*no data in 31 patients

Baseline (i)ADL

Mean baseline (i)ADL was 41 (SD 18.3). (i)ADL was higher in patients with a younger age, a lower ASA classification, those living independently before the fracture and patients who use no walking aid prefracture. (table 2) Gender, prefracture living with a partner and type of fracture were no predictors of baseline ADL.

Table 2; Multivariable analysis of prefracture (i)ADL

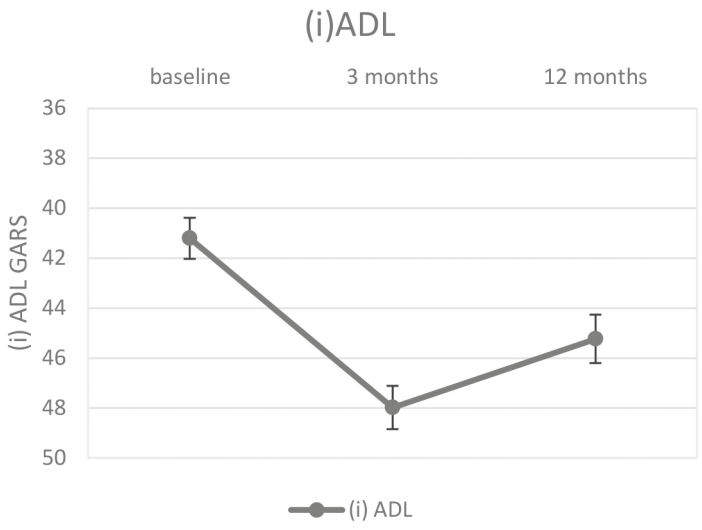
Characteristic	B	Beta	T	Sig
Age	0.10	.06	1.80	.071
ASA classification	5.43	.14	4.88	.000
Prefracture living situation	14.91	.38	12.45	.000
Prefracture use of walking aids	18.22	.51	15.13	.000

Adjusted R square = 0.65

Course of (i)ADL

Figure 3 shows the course of (i)ADL in time. Between baseline and three months (i)ADL declined (thus GARS augmented Δ 6.8 (4.4-9.2) ($p<0.01$)). 95 patients (24%) returned to their prefracture level of (i)ADL after three months. Between three and 12 months (i)ADL recovered (thus GARS declined Δ 2.8 (0.17-5.3) ($p<0.01$)). (i)ADL was still not recovered to baseline value ($p<0.01$). 105 patients (29%) returned to their prefracture level of (i)ADL after 12 months.

Figure 3. Course of (i)ADL in time



The multivariable analyses (table 3) showed that a lower level of (i)ADL (i.e. higher GARS) at three and 12 months postoperative was correlated with higher age, higher ASA classification, living institutionalized before the fracture, prefracture use of walking aids, longer length of hospital stay, having a postoperative complication and a higher prefracture (i)ADL. Gender, prefracture living with a partner and type of fracture were not predictive. General anesthesia was only a predictor of lower (i)ADL at 12 months.

Table 3. Multivariable analysis of (i)ADL at three and 12 months

	Three months				12 months			
	B	**Beta**	**T**	**sig**	**B**	**Beta**	**T**	**sig**
Age	0.13	.08	2.22	.027	0.20	.11	3.22	.001
ASA classification	2.53	.06	2.09	.038	2.69	.06	1.99	.048
Prefracture living situation	4.59	.12	3.20	.001	2.92	.07	1.77	.078
Prefracture use of walking aids	2.58	.07	1.71	.088	3.91	.11	2.39	.017
Type of anesthesia					5.94	.07	2.19	.029
Length of hospital stay	0.32	.17	5.16	.000	0.26	.12	3.70	.000
Postoperative complications	2.85	.08	2.45	.015	3.53	.10	2.83	.005
Prefracture (i-) ADL	0.54	.54	10.75	.000	0.60	.56	10.74	.000

three months; Adjusted R square = 0.69
12 months; Adjusted R square = 0.71

Decline in (i)ADL between baseline and three months was larger in older age, living at home before the fracture, prefracture walking without the use of walking aids and longer length of hospital stay (table 4). Recovery of (i)ADL between three and 12 months was larger in patients prefracture living with a partner and in patients who used no walking aids prefracture.

Table 4. Multivariable analysis of difference in (i)ADL between baseline and three months and between three and 12 months

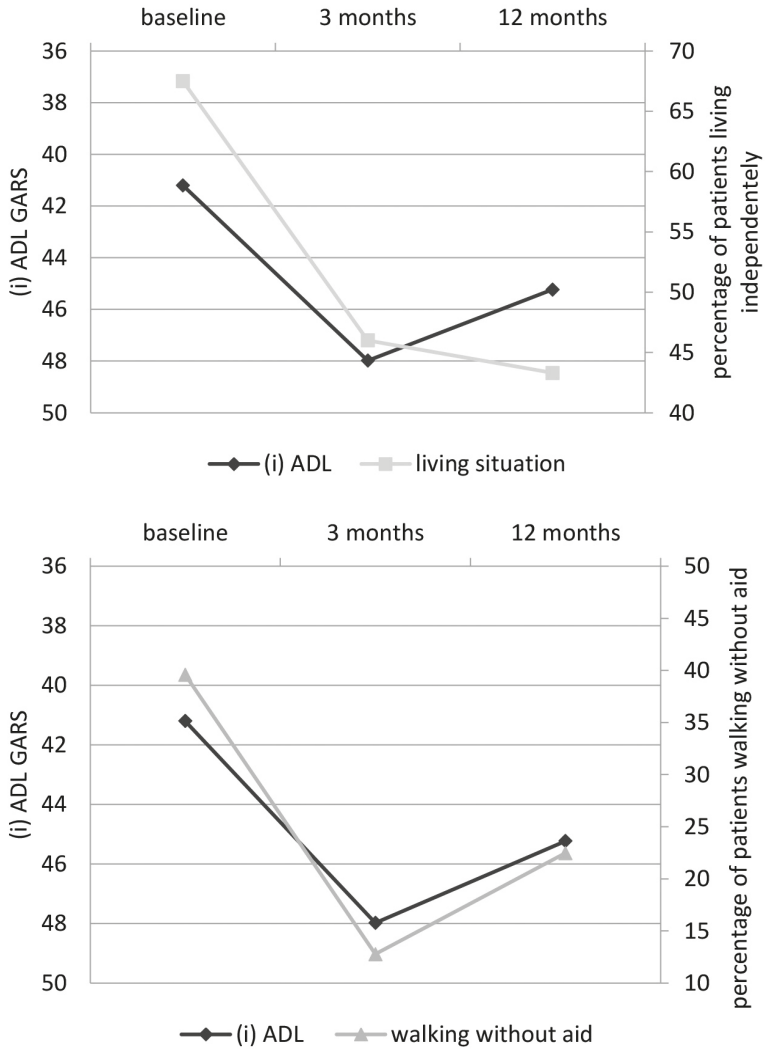
	Difference (i)ADL between baseline and three months				Difference in (i)ADL between three and 12 months			
	B	**Beta**	**T**	**sig**	**B**	**Beta**	**T**	**sig**
Age	0.14	.13	2.27	0.02				
Prefracture living with a partner					1.78	.10	1.80	0.07
Prefracture living at home	2.27	.09	1.68	0.09				
Prefracture use of walking aids	5.50	.24	4.18	0.00	2.84	.97	2.92	0.00
Length of hospital stay	0.26	.21	4.01	0.00				

Difference between baseline and three months; Adjusted R square = 0.08
Difference between three and 12 months; Adjusted R square = 0.04

Correlation between (i)ADL, mobility and living situation.

The percentage of patients mobilizing without a walking aid as well as the percentage of patients who lived independently declined between baseline and three months. (figure 4) While the mobility recovered between three and 12 months postoperative, the percentage of patients living independently did not increase. Correlation between (i)ADL and the percentage of patients living independently for baseline, three months and 12 months together were 0.69 ($p<0.001$) and (i)ADL and the percentage of patients walking without aid 0.80 ($p<0.001$).

Figure 4. (i)ADL and living situation and (i)ADL and walking without aid.



Discussion

This cohort study shows a large loss of (i)ADL after surgical hip fracture treatment: only 29% returned to their pre-operative level of (i)ADL at one year postoperative. Factors associated with a larger loss in (i)ADL after a hip fracture were higher age, prefracture living at home, prefracture not using walking aids and longer length of hospital stay. Furthermore, the association between (i)ADL, mobility and living situation (ie. institutionalized or independed) was high. The latter stresses the

importance of recognizing which patient will be decline in overall functionality and which patient will regain his or hers functionality as good as present at the preoperative level.

The large loss of independence (expressed in a lower level of ADL) after hip fracture treatment has been reported previously. [10, 18, 19] Our study shows that (i)ADL recovers between three and 12 months postoperative, but not to baseline levels, this is in line with the results of earlier studies on recovery of (i)ADL and ADL. [3, 10, 12, 20] In our study prefracture (i)ADL was the most important predictor for a lower (i)ADL at both three and 12 months. This and other significant risk factors (higher age, higher ASA classification, prefracture living institutionalized and prefracture use of walking aids) are signs of increased frailty. A longer length of hospital stay and having a postoperative complication were also associated with lower (i)ADL. A postoperative complication will affect a patient's health and, in that way, will lower his abilities to perform (i)ADL activities. Longer length of hospital stay is usually related to the need for patients of additional care post discharge (like nursery homes). So possibly this factor also partially represents vulnerability.

Two other studies (Mariconda et al. and Gonzalez Zabaleta et al.) investigated predictors for (i)ADL after a hip fracture. Higher age, higher ASA classification and lower prefracture (i)ADL were found as predictors in these studies, which is in accordance with our results. [10, 18] Furthermore Mariconda et al. found that prefracture ambulatory ability and postoperative complications were associated with (i)ADL, like we did. Besides these predictors they found Mini-Mental State Examination (MMSE), post-operative allowance of full weight bearing on the operated limp, surgery within 72 hour, Parkinson and educational status to be associated. [10] These factors were not included in our study. Gonzalez- Zabaleta et al. found type of fracture and surgical delay as other predictors. This study had only a 90 days follow up. [18]

Age, ASA classification, prefracture living situation and use of walking aids were predictors for baseline (i)ADL. Gender, prefracture living with a partner and type of fracture were no predictors for lower baseline (i)ADL in our multivariate analysis, in accordance to other cohort studies. [10, 12, 18] Two previous studies show that an extra capsular fracture is more common in older patients with more comorbidities and lower functional recovery. [21, 22]. Possibly the relation between gender, prefracture living with a partner and type of fracture with the other predictors could have caused that these factors are omitted in our multivariate analysis.

Patients mobilizing without an aid and those living at home before the fracture had greater loss in (i)ADL after their hip fracture. This is in accordance with studies on the same cohort of hip fracture patients as the current study. These studies focussing on of the level of mobility and HRQoL showed that the most mobile patients were least likely to return to their prefracture mobility level and the healthier patients were less likely to return to their prefracture HRQoL level. [23, 24] These healthier and more active patients have more to lose. Type of anaesthesia was no predictor in ADL decline between baseline and three months. Earlier research in large cohort studies confirms this finding. [10, 25] In our cohort general anaesthesia was infrequent (30 patients, 6%) This is mainly due to local guidelines in our hospital.

Recovery in (i)ADL was associated with prefracture mobilising without aid and prefracture living with a partner. Apparently, the presence of a partner contributes to the recovery of (i)ADL. This is in accordance with the study of Koval et al [12] who found that younger age, having no comorbidities and having a partner before the fracture were predictors for recovery of ADL. We noted a moderate to strong association between the level of (i)ADL, living situation and use of walking aids at both baseline, three months and twelve months, which also confirms earlier research. [5] These strong associations underscore the importance of the use of measurements like (i)ADL in hip fracture patients, since they represent a patient's condition. The latter stresses the importance of using these measurements of overall functionality scores in all patients.

The strengths of our study are its prospective character, the size of the cohort and the length of follow up (1 year). Loss of follow-up corrected for mortality was very low: 5% at three months 2% at one year. GARS as instrument to measure (i)ADL has been proven relevant and comprehensive, it has good construct validity and internal consistency. However responsiveness, the minimal clinically important difference (MCID) and ceiling and floor effect are not well known. [15, 16, 26] While this MCID is unknown we do not know whether the statistical differences in the GARS score during follow-up we found, are clinically relevant. A recent review identified 24 existing ADL and (i)ADL questionnaires. [27] The three ADL scores in hip fracture patients that are currently used the most are the Barthel index, Katz ADL and FIM (Functional Independent Measurement.) [28] Comparison with different studies would have been easier using one of these outcome measures. However GARS has the advantage of being a combined list of both ADL and i-ADL. Another limitation is that recall bias might exist on measuring baseline (i)ADL

during admission to the hospital in the emergency department. The patient's ability to recall this prefracture (i)ADL with a painful hip fracture may be questioned, although recent literature showed that recall data is accurate. [29]

In summary, (i)ADL declined after a hip fracture and less than one third of all patients returned to their prefracture level of (i)ADL after three and 12 months. Predictors for lower (i)ADL after a fracture were higher age, higher ASA classification, prefracture living institutionalized, prefracture use of walking aids, longer length of hospital stay, having a postoperative complication and lower prefracture (i)ADL score: i.e. vulnerable patients. However predictors for loss of (i)ADL after an hip fracture were higher age, prefracture living at home, prefracture not using walking aids and longer length of hospital stay: i.e. more healthy patients. Furthermore, the association between the baseline level and decrease of (i)ADL, mobility and livings situation was strong. For that matter, some patients may be identified to have a large decline in their functionality, either due to presence of the hip fracture or invoked by the surgery or the combination of the two. For those hip fracture patients focus may be based only at adequate pain relief in post fracture period. The latter can give a functional outcome without the risk involved with surgery. [30] In the end it is the patient who matters.

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CHAPTER 9

SUMMARY

Hip fracture is increasing, and the consequences can be enormous both for patient as individuals and for the healthcare system of a country. This thesis describes several unfavourable outcomes in hip fracture patients and attempts to predict them. The first part is about arthroplasty and how to use it while minimizing the chance of complications. The second part is about identifying patients at risk for adverse outcomes with regard to mortality, delirium, quality of life and function after the hip fracture.

Part I: (Hemi) arthroplasty

Chapter 2 describes 30,830 hip fracture patients registered with the Dutch arthroplasty register (LROI). These patients were treated with a total hip arthroplasty (THA) (8155 patients) or a hemiarthroplasty (HA) (22,675 patients) between 2007 and 2017. The 1-year revision rate was higher for THA patients, but this is mainly due to confounding by indication; THA patients were younger and had a lower ASA classification and therefore, they were more likely to be fit enough for a potential revision. In the less healthy and older HA population, patients' demand for revision is probably less. Dislocation was the most common reason for revision in both groups (HA 29%, THA 41%). A Cox model in a multivariable approach with competing risk analysis was used to find risk factors for revision of HA and THA. Male sex, age below 80 years, a posterolateral approach and uncemented fixation were risk factors for revision of both HA and THA. Patients with ASA classification III/IV who had THA were revised more often, whereas in the HA cohort, revision was performed more often in ASA I/II patients. These results suggest that uncemented stems and a posterolateral approach lead to higher revision rates.

A multicentre randomised controlled trial of fixation technique in arthroplasty is described in **Chapter 3**. A total of 201 patients 70 years and older with a Garden type III or IV hip fracture were included. They were randomised between a cemented Müller straight stem and an uncemented DB-10 hemiarthroplasty. There were four primary outcome measures described beforehand; complications, operation time, functional outcome and mid-thigh pain. Complications were categorised as major and minor local and major and minor systemic. The major local complications (periprosthetic fracture and dislocation) were more common in the uncemented group (odds ratio; 95% CI) (3.36; 1.40 to 8.11). In the other three primary outcome measures—operation time, functional outcome (timed up and go score and Groningen activity restriction scale) and mid-thigh pain—no differences were observed between groups. Health-related quality of life, measured in this chapter as a secondary outcome, was lower six and twelve weeks after the fracture

in the uncemented group. We conclude that a cemented hemiarthroplasty in elderly patients with a displaced femoral neck fracture results in fewer complications compared to an uncemented hemiarthroplasty.

Part II: Predictors of mortality, delirium, quality of life and daily life functioning after a hip fracture

In **Chapter 4**, we describe an external validation study of a prediction model for mortality in the first 30 days after a hip fracture. This model had been developed previously by other authors as an improvement on the widely used Nottingham Hip Fracture Score (NHFS). We tested the score in our cohort of 422 patients of 70 years and older and found good validity: the area under the ROC curve was 0.70 (95% CI 0.60 – 0.79). Therefore, we concluded that this score can be used to identify patients at risk for early mortality.

Chapter 5 describes a prospective cohort study with 378 hip fracture patients. The department of psychiatry developed a risk model for delirium (RD) based on the published literature at the time. Patients at high risk of delirium according to the RD score were prescribed prophylactic haloperidol (an antipsychotic drug) beginning in 2007. We found no difference in delirium incidence between patients with a hip fracture admitted after 2007 (prophylactic treatment for high-risk patients) and before 2007 (no prophylactic treatment). We concluded that this delirium prevention protocol did not reduce the incidence of delirium.

Chapter 5 further describes the ability of the RD score to identify patients at high risk of delirium. This is possible while all publications we know of have demonstrated that haloperidol does not reduce the incidence of delirium after a hip fracture, therefore the treatment of high-risk patients in our study group has not influenced the delirium incidence in these patients. The area under the ROC curve of the RD score is 0.72 (CI 0.67 - 0.77) (fair). With a cut-off of five, sensitivity of the RD score is 72%, specificity 64%, the negative predictive value 86% and the positive predictive value 42%. Multivariable logistic regression was performed to test the association between the RD score and delirium, length of stay, alternative living situation and mortality. High-risk patients according the RD score had a significant higher incidence of delirium (OR 4.1, CI 2.4-7.0), were more likely to be living at an alternative situation after 3 months (OR 6.6, CI 3.2-13.4) and were less likely to be discharged from the hospital before ten days (OR 1.6, CI 1.0-2.6). The RD score was not associated with mortality. Incidence of delirium in a regression was higher in patients with an RD score ≥5 (OR 4.1, CI 2.4-7.0), male gender (OR 1.9, CI 1.1-3.4)

and higher age (OR 1.0, CI 1.0-1.1). Thus, the RD score is a useful tool to identify patients with a higher chance of delirium.

The RD score that was introduced in Chapter 5 was further analysed in **Chapter 6**. Reliability was tested in 102 patients when a second nurse recorded a RD score for the same patient; intra-class correlation was substantial at 0.77 (0.68–0.84). The optimal cut-off point for balancing sensitivity and specificity was four points (instead of the five points used in Chapter 5). With that new cut-off point, sensitivity was 80% (71–88%), and specificity was 56% (50–62%). Feasibility was tested by controlling all individual RD score sheets for errors compared with the medical chart. In 38 cases, items had a different score than that which would have been concluded from the medical chart (i.e. diagnosis of dementia, age and functional dependence). The clock-drawing test was skipped for 84 patients (22%). Summation of the individual items into the total RD score was incorrect in six patients.

Reliability and validity of the individual items of the RD score were analysed. The item 'use of heroin, methadone or morphine' was positive in nine patients and 'daily consumption of four or more alcoholic beverages' was positive in five patients. Furthermore, the items had low validity (no correlation with delirium); therefore, we propose to remove these items from the RD score. We also propose adding 'male gender' and 'trochanteric fracture' to the score, as these were risk factors for delirium in a multivariable logistic regression (trochanteric fracture OR 1.79 (CI 1.07–3.01) and male gender OR 1.90 (CI 1.06–3.43)).

In **Chapter 7**, health- related quality of life (HRQoL), both the physical and mental components, was measured using the SF-12 in 335 hip fracture patients. Both physical and mental HRQoL declined after a hip fracture, but mental HRQoL recovered after one year to pre-fracture values, while physical HRQoL did not. A logistic regression analysis was performed to identify variables that predict this decline in HRQoL. Age younger than 80 years, ASA classification I or II, higher pre-fracture level of mobility, intracapsular fracture and treatment with osteosynthesis (compared to arthroplasty) were associated with greater decline in physical HRQoL. We could not find any risk factors for greater decline in mental HRQoL.

In **Chapter 8**, 480 hip fracture patients of the same prospective cohort described in Chapter 7 were analysed on their (basic and instrumental) activities of daily living ((i)ADL) using the groningen activity restriction scale (GARS). Relatively few patients returned to pre-fracture levels of (i)ADL: 24% at 3 months and 29% at

1 year. A logistic regression analysis identified higher age, living with a partner pre-fracture, living at home pre-fracture, walking independently pre-fracture and longer length of hospital stay as risk factors for a larger loss of (i)ADL. Living with a partner pre-fracture and use of walking aids pre-fracture were associated with greater recovery of (i)ADL between 3 and 12 months after the fracture. Correlation between (i)ADL, living situation and the use of walking sticks was measured to gain an understanding of the consequences of lower (i)ADL. Correlation between (i) ADL and living situation was substantial (0.69), as was correlation between (i)ADL and mobility (0.80).

CHAPTER 10

GENERAL DISCUSSION

In recent decades, a great deal of effort has been put forth to improve care for geriatric hip fracture patients. Orthogeriatric care models and a shift away from treating displaced femoral neck fractures with osteosynthesis and towards arthroplasty are some examples of these improvements for patients. [1, 2] Despite these efforts, mortality and morbidity after hip fracture remain high. [3, 4] This chapter addresses remaining knowledge gaps and new questions generated by our findings as well as future research perspectives for these often frail patients.

Part I: (Hemi) arthroplasty

In the first part of this thesis, we focused on performing arthroplasty in hip fracture patients with the aim of reducing the percentage of re-operation. The preferred type of fixation of a hip implant (either cemented or uncemented) is still widely debated despite the growing evidence in favour of using cement. In the late 1950s, Sir John Charnley started using polymethylmethacrylate (PMMA) bone cement to fixate the hip prosthesis in the bone. [5] Although PMMA cement has stayed the same, cementation technique has greatly changed over the last 60 years. Cleaning the bone, retrograde insertion and pressurisation are part of these developments. [6] The original cementation technique had a high risk of periprosthetic osteolysis and implant failure. PMMA debris was present in these osteolytic areas; therefore, it was concluded that cement was the cause of the failure and 'cement disease' was recognised as a new entity. [7] The latter coincided with, and likely caused, a vast increase in uncemented implants. From the 1970s on, uncemented components were developed. Occurrence of bone cement implantation syndrome (hypoxia, hypotension and loss of consciousness at the time of cement pressurisation) further stimulated the trend towards use of uncemented implants. [8]

Today, uncemented prostheses are preferred globally, although this choice is not evidence-based. [9–13] Both the register study (Chapter 2) and the randomised controlled trial (Chapter 3) in this thesis identify uncemented stems as a risk factor for revision and major local complications (periprosthetic fractures and dislocation) in hip fracture patients. Recent literature [14] and national guidelines [15, 16] all endorse our findings and advise use of cemented implants in hip fracture patients. Despite this evidence, the register study in Chapter 2 shows that in the Netherlands, 34% of hemiarthroplasties and 57% of the total hip arthroplasties are placed without cement. This predominance in the use of uncemented implants is higher than in other European countries: in the UK, Wales and Northern Ireland, 27% of hemiarthroplasties were uncemented, in Norway 22%, and in Sweden, only 5%. [17, 18]

The register study in Chapter 2 also found that a posterolateral approach is a risk factor for revision. This finding is in accordance with national guidelines [15, 16] and recent publications [19, 20] that advise against the use of the posterolateral approach in hip fracture patients. Despite the evidence, a large percentage of Dutch orthopaedic surgeons do not adhere to these guidelines: 55% of patients are treated using a posterolateral approach (Chapter 2). The reason for this low implementation rate might be that the new Dutch guidelines were published only a year before the end of our study, which included patients from 2007 until 2017. The old guidelines [21] had no preference as to surgical approach. In contrast to the current Dutch guidelines, data from the Norwegian register indicate that a posterior approach results in less pain, fewer walking problems and better QoL than a lateral approach. [22] A more recent trend is the use of dual mobility cups to reduce the dislocation rate present in a posterolateral approach; this seems logical, but has yet to be evaluated. [23]

Finally, there can be valid reasons to deviate from protocol and use a uncemented stem or a posterolateral approach in specific circumstances, such as the experience of a surgeon or a centre or the specific needs of a patient. Nevertheless, for 57% of hip fracture patients to receive an uncemented total hip is, in our opinion, unexplainable.

Future perspectives

More research on the best fixation technique for hip fractures will not yield new insight. Effort should be spent on improving implementation of the new guidelines amongst hip fracture surgeons. A feedback of registry outcome to individual surgeons is a good tool to accomplish this goal. Changes to practice may be met with scepticism, but can be made with the appropriate training and implementation strategy. [24–26]

More research should be conducted on the best approach in both total and hemiarthroplasty in hip fracture patients. The anterior approach should be included in these analyses. Even as more evidence becomes available, surgeons will continue to have their own opinions and preferences on the best approach in their hands. Although these opinions have some basis in truth, they need to be validated with rigorous analysis of data. Data are available from the Dutch Arthroplasty Register (LROI), with sub-analyses and feedback to groups of surgeons on their performance with respect to the benchmarks. Only then will patient outcomes improve.

Part II: Predictors of mortality, delirium, quality of life and daily life functioning after a hip fracture

The number of hip fractures is expected to increase, placing a heavy burden on health care costs. Thus, it is important to establish prevention programmes and to target care programmes to specific patient groups. For the latter, it is necessary to be able to predict outcomes for specific patient groups. In this thesis, we also aimed to predict mortality, delirium, quality of life and daily life functioning after hip fractures based on pre-fracture characteristics in a relatively large cohort of hip fracture patients.

The one-year mortality rate for patients who sustain a hip fracture is high, and patients living in a nursing home when the fracture occurs have the highest mortality rate. [27] The Almelo Hip Fracture Score (AHFS) aims to identify patients at intake who have a higher risk of mortality. Chapter 4 showed that the AHFS was valid in an external validation. The knowledge of mortality risk can be used to inform doctors, patients and families who have to make difficult choices on whether a patient, considering his comorbidities, should be operated on or receive non-surgical pain relief without a surgical procedure. [28]

In addition to focussing on the hip fracture itself, identifying the group of hip fracture patients at high risk for delirium early after hospital admittance can improve overall outcome in these patients. Some interventions exist to prevent delirium in high-risk patients, such as monitoring anaesthetic depth with Bi Spectral Index (BIS) and multi-component interventions (like oxygen therapy, fluid intake management, pain relief management and avoidance of polypharmacy) [29, 30] Since some of these interventions are expensive, they should be targeted only to patients at high risk for developing delirium. By 2012, 37 risk prediction models for delirium had already been published. [31] However, most of these prediction models are not applicable to hip fracture patients or require too much time and specific skills (e.g. APACHE II, MMSE scores) to be used in daily clinical practice. [32–34] A prediction model should be simple and quick. The RD score, presented in Chapter 5, meets these requirements and has good reliability and validity. With slight changes, namely adding some risk factors and changing the cut-off point, the reliability and validity could be improved even further. However, external validation of this new delirium prediction model should be conducted prior to implementation.

Prophylactic treatment with haloperidol did not reduce the incidence of delirium in hip fracture patients (Chapter 4). The Dutch guidelines on delirium advise use

of non-pharmacologic measures as the standard to prevent delirium and only to consider using prophylactic medication in high-risk patients. Only low-quality evidence exists for the preventive use of haloperidol, which might have an effect on the depth and duration of the delirium. [35, 36] More research is needed on whether pharmacologic prophylactic treatment should be started and what treatment is most effective.

The physical domain of Health Related Quality of Life (HRQoL) and Activities of Daily Living ((i)ADL) declined in the first three months after a hip fracture (Chapters 7 and 8). These data indicate the enormous impact a hip fracture has on a patient's life. Younger age, lower ASA classification, higher pre-fracture level of mobility, intracapsular fracture and treatment with osteosynthesis (compared to arthroplasty) predicted larger decline in HRQoL. Older age, living with a partner pre-fracture, living at home pre-fracture, and walking independently pre-fracture predicted larger decline in (i)ADL. Interestingly, the most vulnerable patients were not the ones who experienced the greatest decrease in HRQoL and (i)ADL scores. Therefore, we hypothesise that healthier hip fracture patients have more to lose and therefore, this patient group requires attention. This hypothesis is strengthened by the results of the Trondheim hip fracture trial, in which comprehensive geriatric care had the greatest positive effect on younger patients with a higher pre-fracture (i)ADL level. [2] In this thesis, we evaluate a decline in patients' outcome parameters (HRQoL and (i)ADL) between the pre-fracture state and the 3 months post-operative state. Analysing the change score between the pre-intervention and post-intervention states identifies those patients who declined most in their HRQoL and (i)ADL. These patients will probably benefit most from targeted care, such as home-based rehabilitation and comprehensive geriatric care. [2, 37] Using a change score between the pre-fracture and the post-fracture state will not identify those patients with the lowest HRQoL and (i)ADL. Analysing this change score data will give clues on how best to shape policy to improving outcomes for the most vulnerable patients.

Future perspectives

Machine learning techniques combining encrypted data on thousands of patients from different sources (e.g., nursing home files, general practitioner files, hospital data, biomarkers, arthroplasty databases) will generate prediction models on outcomes such as mortality, ADL and HRQoL. These machine learning algorithms place a certain probability on outcomes and can thus be used in clinical decision-making by both the physician as well as the patient, who can decide whether he or

she accepts the risk to realize the benefit. [38] Machine learning appears to have a higher predictive accuracy than multivariate regression models (such as the ones presented in this thesis), because machine learning algorithms can use complex (non-linear) relations within data. [39] But the validity of the prediction will always depend on the validity of the data source. For that matter, also real-world data (i.e., national registry data) is biased compared to a careful constructed cohort: there can be selection bias and confounding by indication. Or, as Kilkenny put it, 'Garbage in – Garbage out'. [40] Nevertheless, these national registry data are essential in comparing outcome data. This will improve patient outcome after interventions.

More papers are reporting prediction models, but these are often based on small cohorts. Van Meenen et al. found 37 post-operative delirium risk prediction models, and Karres et al. compared six different prediction models for mortality. [31, 41] Developing new prediction models from existing cohorts will generate more publications but is probably of less added value for patient care. It is more important to select existing models that are valid, easy, fast and inexpensive and to evaluate these models in external cohorts. [31, 42]

When comparing data, agreement must be reached on the best available outcome score that is valid and easy to score. European guidelines have designated the EQ5D score as the preferred outcome measurement for HRQoL. [43] The Barthel index and FIM score are the most used ADL scores; therefore, researchers are advised to use them as outcome parameters in future studies. [44] Uniform outcome data enables patients and insurance companies to compare delivered care between hospitals (assuming case mix is taken into account). To achieve that, outcome parameters should be measured after every hip fracture. In the Netherlands, measuring outcome in survival has been abandoned by the health inspection since 2015. Instead, re-operation, a mobility score (based on the Parker mobility score) and the Katz-ADL score have been implemented as standard outcome measurements. [45] Surgeons must provide ADL data from all their hip fracture patients pre-fracture and 3 months post-fracture to the Dutch Hip Fracture Audit (DHFA). This database is not fully linked to the LROI database or to hospital electronic patient files. Problems with data collection also render the mobility and ADL scores far from being valid in this hip fracture patient population. Caution is needed so as not to overload clinicians and patients with administrative paperwork.

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10

CHAPTER 11

NEDERLANDSE SAMENVATTING

Het aantal heupfracturen stijgt en de gevolgen van een heupfractuur kunnen voor zowel de patiënt als voor de gezondheidszorg immens zijn. Dit proefschrift beschrijft aspecten van de slechte uitkomsten van heupfracturen en tracht een aantal antwoorden hierop te geven. Het eerste deel gaat over prothesiologie en hoe dat toe te passen met de kleinste kans op complicaties. Het tweede deel gaat over het identificeren van patiënten die een slechtere uitkomst hebben op het gebied van overleven, delier, kwaliteit van leven en functie na een heupfractuur.

Deel I: prothesiologie

In **hoofdstuk twee** beschrijven we 30.830 patiënten die voor een heupfractuur behandeld zijn met een prothese en geregistreerd zijn in de Landelijke Registratie Orthopedische Implantaten (LROI). Tussen 2007 en 2017 werden 8155 patiënten behandeld met een totale heupprothese (THP) en 22.675 met een kophalsprothese (KHP). Het 1-jaars revisie percentage was hoger in de THP-patiëntengroep, de oorzaak hiervoor is waarschijnlijk het verschil in indicatiestelling. De THP-patiënten waren jonger en hadden een lagere ASA-classificatie en waren dus fitter om een eventuele revisie te ondergaan. Bij de oudere en minder gezonde KHP-patiënten is de vraag naar revisie waarschijnlijk minder en de drempel hoger. De meeste revisies werden verricht vanwege luxatie (41% THP, 29% KHP). We gebruikten een multivariabele analyse met competing risk analysis om risicofactoren voor revisie te vinden bij zowel THP als KHP. Man, leeftijd jonger dan 80 jaar, posterolaterale benadering en ongecementeerde prothese waren risicofactoren voor revisie in zowel THP als KHP. Hogere ASA-classificatie was bij THP een risico voor revisie, lagere ASA-classificatie was bij KHP een risicofactor voor revisie. Deze studie suggereert dat gebruik van ongecementeerde stelen en een posterolaterale benadering bij heupfractuurpatiënten leidt tot meer revisies.

Hoofdstuk drie beschrijft een multicenter gerandomiseerde trial over de fixatiemethode van prothesen bij heupfractuurpatiënten. 201 patiënten van 70 jaar en ouder met Garden type III- of IV-heupfractuur werden geïncludeerd. De patiënten werden gerandomiseerd tussen een gecementeerde Müllerprothese en een ongecementeerde DB-10 KHP. Vooraf werden vier verschillende primaire uitkomstmaten bepaald. Eén daarvan was complicaties, waarbij de grote lokale complicaties (zoals periprothetischefracturen en luxatie) meer voorkwamen in de ongecementeerde groep (odds ratio; 95% CI) (3.36; 1.40 tot 8.11). De andere drie primaire uitkomstmaten waren operatieduur, functionele resultaten (Timed Up and Go score en Groningen Activity Restriction Scale) en mid-thigh pain. Deze lieten allemaal geen verschil zien tussen de gecementeerde en de ongecementeerde

prothesen. Gezondheid gerelateerde kwaliteit van leven (HRQoL), die in deze studie als secundaire uitkomstmaat werd gemeten, was zes en twaalf weken na de breuk lager in de ongecementeerde groep. In dit hoofdstuk wordt geconcludeerd dat gebruik van ongecementeerde prothesen tot meer complicaties kan leiden.

Deel II: voorspellers van uitkomst: mortaliteit, delier, kwaliteit van leven en functioneren

Mortaliteit en morbiditeit is hoog in de patiëntengroep die een heupfractuur oploopt. In het tweede deel van dit proefschrift kijken we naar voorkomen van delieren. Ook kijken we naar welke risicofactoren een delier, een verslechtering in kwaliteit van leven, dagelijks functioneren en mobiliteit kunnen voorspellen.

Hoofdstuk vier beschrijft een externe validatie studie van een risicoscore welke de mortaliteit binnen 30 dagen voorspelt. Deze score, welke een variatie is op de Nottingham Hip Fracture Score, is ontwikkeld in Almelo. In dit extern validatieonderzoek is de Almelo Hip Fracture Score toegepast op het Delftse cohort (422 patiënten van 70 jaar en ouder). Er werd een acceptabele validiteit gevonden, gebied onder de ROC curve was 0.70 (95% CI 0.60 – 0.79)). Hiermee kan geconcludeerd worden dat de Almelo Hip Fracture Score valide is.

Delier is een veel voorkomende complicatie na een heupfractuur. In 2004 werd door de afdeling psychiatrie in het Reinier de Graaf Gasthuis een Risicoscore voor Delier (RD) ontwikkeld op basis van op dat moment bekende risicofactoren voor delier. Vanaf 2007 werden patiënten met een hoog risico op delier volgens deze RD profylactisch met Haloperidol (een antipsychotica) behandeld. In **hoofdstuk vijf** hebben we de delier incidentie vergeleken tussen de patiënten met een heupfractuur voor 2007 (geen profylaxe bij hoog-risicopatiënten) en na 2007 (wel profylaxe bij hoog- risicopatiënten). Er was geen verschil in delier incidentie. We kunnen concluderen dat er geen aanwijzingen zijn dat delierprofylaxe middels Haloperidol bij hoog- risicopatiënten de incidentie van delier verlaagd.

In **hoofdstuk vijf** wordt ook de validiteit van de RD beschreven. Het gebied onder de ROC-curve was 0.72 (CI 0.67 – 0.77) (fair). Wanneer een afkappunt van vijf punten werd gekozen dan was de sensitiviteit 72%, de specificiteit 64%, de negatief voorspellende waarde 86% en de positief voorspellende waarde 42%. Een multivariabele logistische regressie werd uitgevoerd om de associatie tussen de RD en delier, opnameduur, ontslag naar een andere woonsituatie en mortaliteit te testen. Patiënten met een hoog risico op delier volgens de RD hadden een hogere

delierincidentie (OR 4.1, CI 2.4-7.0), woonden 3 maanden na opname vaker in een andere woonsituatie dan daarvoor (OR 6.6, CI 3.2-13.4) en hadden vaker een opnameduur van meer dan 10 dagen (OR 1.6, CI 1.0-2.6). Er was geen associatie met mortaliteit. De incidentie van delier was hoger bij patiënten met een RD-score groter dan 5 (OR 4.1, CI 2.4-7.0), mannelijk geslacht (OR 1.9, CI 1.1-3.4) en hogere leeftijd (OR 1.0, CI 1.0-1.1). Uit hoofdstuk vijf kunnen we daarom concluderen dat de RD een goed instrument is om patiënten met een hoog risico op delier te identificeren.

Verder analyse van de RD vindt plaats in **hoofdstuk zes**. De betrouwbaarheid werd getest door bij 102 patiënten de score tweemaal door twee verschillende verpleegkundigen af te laten nemen; de intraclass correlation was substantieel; 0.77 (0.68 – 0.84). De validiteit was redelijk. Het optimale cutoff punt, om de sensitiviteit en specificiteit in balans te brengen, was vier punten (in plaats van de vijf punten gebruikt in hoofdstuk vijf). Bij gebruik van dit nieuwe cutoff punt was de sensitiviteit 80% (71 — 88%) en de specificiteit 56% (50 — 62%). De haalbaarheid (feasibility) werd getest door de individuele RD-lijsten te controleren op fouten op basis van de medische status van patiënten. 38 keer werd een andere score ingevuld dan juist zou zijn op basis van de status (bijvoorbeeld de diagnose dementie of de leeftijd). Het tekenen van een klok werd bij 84 (22%) patiënten overgeslagen. Door zes patiënten werden de items van de RD verkeerd opgeteld. Ook de individuele items van de RD werden getest op validiteit en betrouwbaarheid. 'Gebruik van heroïne, methadon of morfine' was slechts positief bij negen patiënten en 'dagelijks gebruik van vier of meer alcoholische dranken' was positief bij vijf patiënten. Bovendien hadden deze items een lage validiteit. Daardoor werd voorgesteld deze items in het vervolg uit de RD te halen. Mannelijk geslacht en extracapsulaire fractuur zouden toegevoegd kunnen worden aan de RD omdat ze in een multivariabele logistische regressie naast de RD-score voorspellers waren voor delier (extracapsulaire fractuur OR 1.79 (CI 1.07–3.01) en mannelijk geslacht OR 1.90 (CI 1.06–3.43)).

In **hoofdstuk zeven** werd de SF-12 vragenlijst gebruikt om zowel de fysieke als de mentale kwaliteit van leven te meten bij 335 patiënten met een heupfractuur. Zowel de fysieke als de mentale kwaliteit van leven namen af na een heupfractuur. De mentale kwaliteit van leven nam na een jaar weer toe tot het niveau van voor de breuk, de fysieke kwaliteit van leven bereikte dit niveau niet meer. We voerden een logistische regressie uit om te zien welke factoren het verlies van kwaliteit van leven konden voorspellen. Leeftijd jonger dan 80 jaar, ASA-classificatie I en II, meer mobiliteit, een intracapsulaire fractuur en behandeling met osteosynthese

(in tegenstelling tot een prothese) waren risicofactoren voor een groter verlies in kwaliteit van de fysieke kwaliteit van leven. Er kon met dit model geen risicofactoren gevonden worden voor het verlies van mentale kwaliteit van leven.

Van het cohort heupfractuurpatiënten, waar in hoofdstuk zeven de kwaliteit van leven van werd bestudeerd, is in **hoofdstuk acht** het dagelijks functioneren onderzocht. De Groningen Activity Restriction Scale is gebruikt om zowel het basisfunctioneren (zelfverzorging) en instrumentaalfunctioneren (nodig voor het leven in de samenleving) te meten. Slechts 24% herstelde in functioneren drie maanden na de breuk en 29% na een jaar. Een logistische regressie liet zien dat hogere leeftijd, het hebben van een partner, thuis wonen, meer mobiliteit en langere ziekenhuisopname geassocieerd waren met een groter verlies van functioneren. Herstel van functioneren tussen drie en twaalf maanden was geassocieerd met het hebben van een partner en meer mobiliteit voor de breuk. In dit hoofdstuk hebben we ook berekeningen gemaakt over de samenhang tussen functioneren, woonsituatie en mobiliteit om een indruk te kunnen geven over de impact van een laag functieniveau. De correlatie tussen functioneren en woonsituatie (0.69) en tussen functioneren en mobiliteit (0.80) was substantieel.

APPENDICES

List of publications

Publications related to the research of this thesis:

Delirium risk screening and haloperidol prophylaxis program in hip fracture patients is a helpful tool in identifying high-risk patients, but does not reduce the incidence of delirium.
Vochteloo A.J.H., Moerman S., van der Burg B.L., de Boo M., de Vries M.R., Niesten D.D., Tuinebreijer W.E., Nelissen R.G.H.H., Pilot P.
BMC Geriatr. 2011 Aug 11;11:39.

Validation of the Risk Model for Delirium in hip fracture patients.
Moerman S., Tuinebreijer W.E., de Boo M., Pilot P., Nelissen R.G.H.H., Vochteloo A.J.H.
Gen Hosp Psychiatry. 2012 Mar-Apr;34(2):153-9.

More than half of hip fracture patients do not regain mobility in the first postoperative year.
Vochteloo A.J.H., Moerman S., Tuinebreijer W.E., Maier A.B., de Vries M.R., Bloem R.M., Nelissen R.G.H.H., Pilot P.
Geriatr Gerontol Int. 2013 Apr;13(2):334-41

Factors associated with the course of health-related quality of life after a hip fracture.
Moerman S., Vochteloo A.J.H., Tuinebreijer W.E., Maier A.B., Mathijssen N.M.C., Nelissen R.G.H.H.
Arch Orthop Trauma surg 2016 jul; 136 (7)

Cemented versus uncemented hemiarthroplasty of the hip as a treatment for a displaced femoral neck fracture: a randomised controlled trial.
Moerman S., Mathijssen N.M.C., Niesten D.D., Riedijk R., Rijnberg W., Koëter S., Kremers van de Hei K., Tuinebreijer W.E., Molenaars T., Nelissen R.G.H.H., Vochteloo A.J.H.
BMC Musculoskelet Disord. 2017 Apr 21;18(1):169

Only 29% of patients return to their prefracture level of (instrumental) Activities of Daily Living after a hip fracture. A prospective cohort study of 480 patients.
Moerman S., Vochteloo A.J.H., Tuinebreijer W.E., Mathijssen N.M.C., Nelissen R.G.H.H.
Geriatr Gerontol Int. 2018 Jul 13

Hemiarthroplasty and total hip arthroplasty in 30,830 patients with hip fractures: data from the Dutch Arthroplasty Register on revision and risk factors for revision.
Moerman S., Mathijssen N.M.C., Tuinebreijer W.E., Vochteloo A.J.H., Nelissen R.G.H.H.
Acta Orthop., 2018 Aug 6:1-6

External validation of the Almelo Hip Fracture Score (AHFS), a prediction model for early mortality following hip fracture surgery
Moermans S. Wesdorp T.M., Vochteloo A.J.H., Mathijssen N.M.C.
Submitted

Other publications:
Repositie van supracondylaire humerusfracturen middels een tijdelijke Kirschner-draad.
Moerman S., Buisman F.E., Schütte P.R., Punt B.J.
Ned Tijdschr Traum 2015 - nr 2, 25-29

A woman with swollen shoulders.
Moerman S., Vis M., Colaris J.C.
Ned Tijdschr Geneeskd. 2018 Dec 17; 163 pii: D3111.

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Curriculum vitae

Sophie Moerman werd geboren op 7 oktober 1985 in Rotterdam. In 2002 haalde zij haar vwo-diploma op het Krimpenerwaard College in Krimpen aan den IJssel. Hierna studeerde zij geneeskunde aan de Erasmus Universiteit in Rotterdam. Haar traumatologiecoschap volgde ze in Kaapstad, Zuid-Afrika. Tijdens haar keuze-coschap orthopedie in 2009 in het Reinier de Graaf Gasthuis is ze betrokken geraakt bij het onderzoek van dr. A.J.H. Vochteloo naar de nasleep van een collumfractuur. Ze is bij dit onderzoek betrokken gebleven tijdens haar werk als arts niet in opleiding in het Albert Schweitzer ziekenhuis, Dordrecht en het Reinier de Graaf Gasthuis, Delft. Ook tijdens haar opleiding tot orthopedisch chirurg in het Albert Schweitzer ziekenhuis (opleider dr. P.W. Plaisier), het Erasmus MC (opleiders prof. dr. J.A.N Verhaar en dr. P.K. Bos) en Reinier de Graaf Gasthuis (opleider dr. R. M. Bloem) heeft ze dit onderzoek gecontinueerd. Na afronding van haar opleiding is ze in 2018 begonnen als fellow kinderorthopedie in het Universitair Medisch Centrum in Groningen, waar ze op dit moment met haar gezin woont. Naast haar interesse in de orthopedie zoekt ze ook sportieve uitdagingen. Zo heeft ze de Dolemietenmarathon gefietst en de alternatieve Elfstedentocht geschaatst. Ze is al 15 jaar lid van de vereniging Friesche Elfsteden in de hoop deze ooit nog eens te mogen schaatsen.