OUTCOME AFTER HIP FRACTURE IN OLDER PATIENTS

medical decision-making, quality of life and societal impact

Marc van de Ree

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“Primum non nocere”

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CHAPTER 1

General introduction and outline of this thesis

A hip fracture is a potentially devastating injury for older adults. Older adults after hip fracture often have poor outcomes, including pain, functional decline, delirium, institutionalization and death[1,2]. The mechanism of injury is a low energetic trauma, usually a fall directly onto the hip. Older adults are at an increased risk of sustaining a hip fracture after a fall incident, especially due to osteoporosis[3].

The history of the development of a treatment rationale for hip fractures parallels the historical development of orthopaedic surgery itself and started with a nonoperative approach. Ambroise Paré (c. 1510 – 1590), a famous French barber surgeon in the Renaissance, reported the first hip fracture in medical literature in 1575[4]. Until the 19th century, hip fracture was considered to be incurable and surgeons followed the directive of Sir Astley Cooper (1768-1841), one of Britain's surgical authorities, to 'treat the patient and let the fracture go'. Discussions concentrated primarily on the position and immobilization of the injured limb. Cooper created the first classification in 1822 to classify intracapsular- (femoral neck fractures; Figure 1) and extracapsular (pertrochanteric; Figure 2) hip fractures[5]. He proclaimed that the blood supply in intra-capsular fractures was insufficient and fragments were too unstable and claimed that all intra-capsular fractures were incurable. At that time older patients treated with any regimen were bedridden, old and likely to expire from bedsores and exhaustion, and then died. To protect both the patient and the clinicians' reputation, he consequently advised that the only realistic therapeutic goal was palliation.

However, on 1 June 1882, Dr. Nicholas Senn presented a specimen with an example of a healed intra-capsular hip fracture[6]. It resulted in further attempts at surgical innovation to restore affected patients and showed that it might not be entirely futile. In 1894 J. Nicolaysen (1831-1911), Professor of Surgery at the National Hospital, Oslo, performed the first closed nailing of a fracture of the femoral neck. He published this technique and the results of 21 patients, and he is recognized in the international literature as a pioneer in the operative treatment of fracture of the femoral neck[7]. In 1931, Smith-Petersen using a nail of biocompatible metals from Venable and Stuck and was simplified by the introduction of the cannulated nail by Johansson in 1932, and these improvements were essential steps in the success of this technique[8,9]. In 1940, Moore and Bohlman introduced a stainless steel hemiarthroplasty and accelerated the treatment of intracapsular fractures[10]. Nowadays in younger fit patients with a femoral neck fracture total hip arthroplasty may lead to higher patient-centered outcomes[11]. Also for extracapsular fractures, in 1939 was the beginning point for the breakthrough of

closed intramedullary nailing introduced by Küntscher and leads in 1988 to the first fixation device allowing full weight-bearing in those fractures[12].

However, despite these advances in the treatment of hip fractures, in vulnerable patients we must still refer to this entity as the famous term 'the unsolved fracture', introduced by Kellogg Speed (1879-1955), due to associated morbidity and high mortality rates.

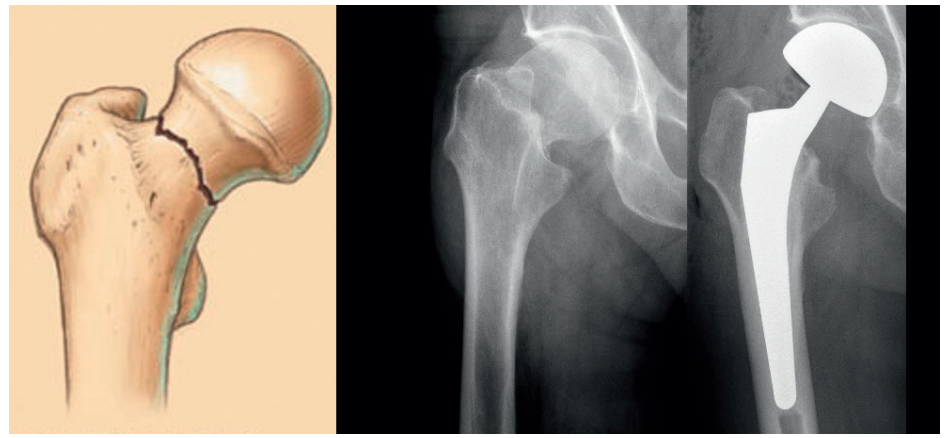

Figure 1. Intracapsular hip fracture treated with a hemiarthroplasty

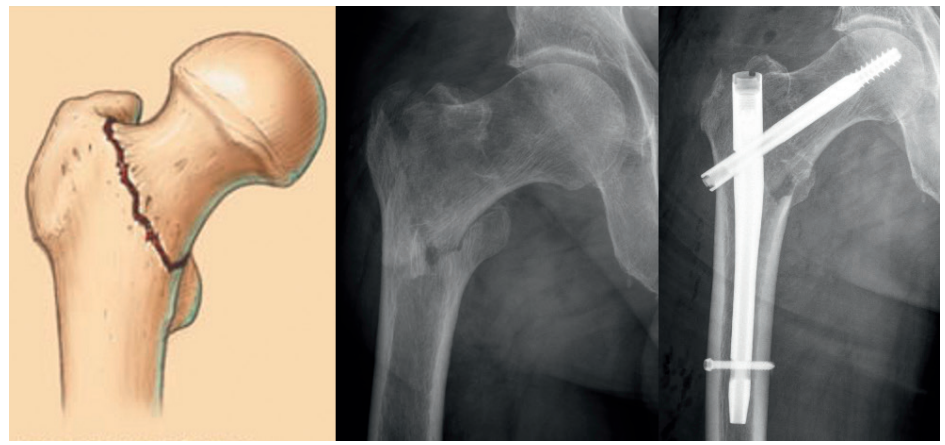

Figure 2. Extracapsular hip fracture treated with an intramedullary nail

CURRENT ISSUES

The public health burden of hip fractures may continue to grow due to aging, and worldwide 4.5 million people are disabled from hip fractures each year. It is expected to increase to 21 million persons living with this disability each year by 2050 with estimated worldwide direct and indirect costs of USD 131 billion[13,14]. In the Netherlands the annual healthcare costs for hip fractures are approximately between €19,741 and €26,355 per person[15-18], and will increase with 50% by 2030[19]. Most research in hip fractures was initially based on technical aspects of hip fracture management and outcome assessment was focused on mortality rates, time to surgery, length of stay, surgical implant success or operative complications[20]. Nowadays researchers have started addressing clinical and functional outcome of hip fractures in vulnerable older adults. However, the outcome of a patient after hip fracture is only partially related to successful management of the fracture. In vulnerable older patients medical decision-making is becoming increasingly important and offered an opportunity to discuss palliative care. Palliative care focuses on improving Quality of Life (QoL) for patients and relatives by providing an added layer of support, including goals of care discussions, pain and symptom management, care planning and coordination, and end-of-life care[21,22]. Especially considering a hip fracture is a prototypical geriatric illness and is associated with worse clinical outcomes, research is needed to aid healthcare providers, patients and relatives in medical decision-making.

OUTCOME ASSESSMENT

Mortality following hip fracture is high and well reported in several clinical studies. In general, 30-day mortality is described between 10% and 13% and 1-year mortality is described between 22% and 33%[23]. Mortality is subsequently higher among nursing home residents than among community dwellers, scientifically substantiated with a reported six-month mortality of 36.2% in nursing home residents in general and 55% within nursing home residents with end-stage dementia, and a four-month mortality of 38.1% in extremely elderly[24-26].

Comorbidities significantly impact the patient outcomes after hip fracture. Preoperative examination and assessment are required to determine patients' baseline medical condition and identify decompensated or previously unrecognized conditions. The vast majority of hip fracture patients aged 65 years and older and three-quarters of all hip fractures occur in women[27]. Adults aged 85 years and older are more than 10 times likely to sustain a hip fracture than those aged 65 to 69 years[28]. In a general older population (age ≥80 years) 78% have two or more medical conditions existing simultaneously[29]. Patients with a hip fracture have frequently multiple comorbidities and geriatric problems related to physical, mental, functional and social conditions. Understanding geriatric principles are extremely important for healthcare professionals treating these older patients multidisciplinary and to anticipate in issues involved in the aging patient. A special focus on the "phenotypic approach" will further enhance care to assess outcome in older patients with a hip fracture. Fried et al. described a "phenotypic approach" by frailty, which is theoretically defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems[30,31]. It suggests that a critical mass of impairments or geriatric conditions add up to the phenotype of frailty, more than any disease or comorbidity[32]. The consideration of older adults' frailty status is fundamental to their care. For example, a severely frail 73-year-old person may not survive hip fracture surgery, even though they are comparatively young, and may benefit more from surgery based on age. Likewise, a fit 86-year-old might well withstand such a surgical procedure despite being older. Outcome assessment could provide information for future risk assessment to aid healthcare providers, patients and relatives in medical decision-making in individual patients in order to optimize quality of care.

Frail patients with a hip fracture frequently suffer from profound cognitive and functional disability and have a limited life expectancy[24,33]. A systematic review reported 19.2% of people with a hip fracture meet formal diagnostic criteria for dementia and 41.8% were cognitively impaired[34]. With the growing number of hip fractures in patients with dementia or cognitive impairment the clinical management will most likely involve a relative, by virtue of the patient's lack of capacity before, during or after an acute deterioration. Nonetheless, recently published large clinical studies about hip fractures, such as FAITH (Fracture fixation in the operative management of hip fractures)-trial and HEALTH (Hip fracture evaluation with alternatives of total hip arthroplasty versus hemiarthroplasty)-trial, have commonly excluded patients with dementia and

cognitive impairment[35]. In our Brabant Injury Outcome Surveillance (BIOS) also frail and cognitively impaired patients were included by means of a proxy respondent to assess outcomes based on proxy reports. The BIOS is a prospective observational follow-up cohort study assessed psychological, social and functional outcome, and costs after trauma during 12 months follow-up within all injured patients admitted in 1 of 10 hospitals in the county Noord-Brabant, the Netherlands[36]. We used a subset of patients with hip fractures, including patients with femoral neck fractures and pertrochanteric fractures, aged ≥65 years with an Injury Severity Score ≤13.

QUALITY OF LIFE, PSYCHOLOGICAL DISTRESS AND SOCIETAL BURDEN

In order to make an appropriate estimation of the impact of a hip fracture a wide range of patient- and proxy reported outcomes (PROs) are used in the BIOS. Examples of PROs are QoL, health-related QoL (HRQoL) and health status (HS). These are all self-reported (i.e. subjective) and multidimensional assessing at least three domains: physical, psychological, and social. Long-term disability is common among patients after a hip fracture and improvement in overall QoL is a major outcome of recovery. QoL, broader than health, is a multidimensional concept including both positive and negative aspects of life, and it measures patients' evaluation of functioning in line with their expectations[37]. QoL in older people is limited by an individuals' loss of ability to pursue different attributes with regard to attachment, role, enjoyment, security and control[38]. This multidimensional concept can be measured with a capability wellbeing instrument in older adults following a hip fracture[39,40]. HRQoL is more narrowly defined and the focus is on those QoL components, such as physical, emotional and social well-being, that are impacted by a disease or condition. HS is also seriously affected by a hip fracture[41]. HS assesses physical possibilities, state of mind and social activities without an evaluation or feelings about functioning[42] and can be measured with a generic instrument[43]. Figure 3 shows the relationship between QoL and related concepts.

A substantial proportion of patients with a hip fracture experienced psychological distress[44]. Psychological distress is a general term to describe a negative internal state of the individual that is dependent on interpretation or appraisal of threat, harm, or demand[45]. It is a broader concept than subclinical anxiety and depression, but it could be characterized by symptoms of depression, symptoms

of anxiety and symptoms of posttraumatic stress (PTS)[46]. The presence of psychological distress is associated with an increased risk of mortality, prolonged length of hospital stay, more physical dependence, chance of discharge to a residential or nursing home and uncertain prospects of recovery after a hip fracture[47-49].

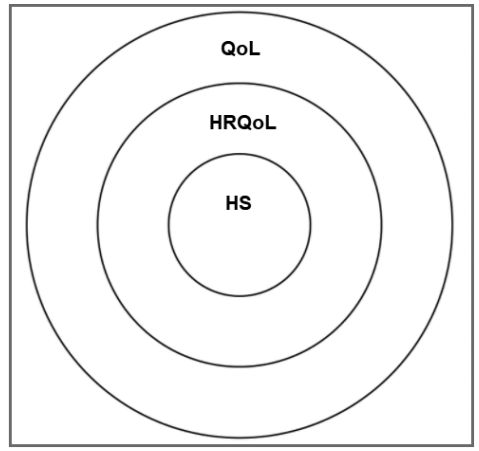

Figure 3. Conceptualisation of Quality of Life (QoL), health-related Quality of Life (HRQoL) and health status (HS)

Knowledge on the course of QoL, HS and psychological distress could give patients guidance on what to expect of their trajectory after a hip fracture. To improve our knowledge on these outcomes clinicians could identify patients at risk of a poor outcome and could determine which patient needs additional care, better monitoring or change of treatment.

Another important focus is societal burden. Hip fractures result to burden in patients primary, but also leads to caregiver burden and burden on the healthcare system. A hip fracture is one of the most important causes of hospital admissions among older patients and leads to a loss of independence. These patients belong to one of the larger groups in society that suddenly need informal care for a shorter or longer period. According to data of the Dutch Ministry of Healthcare, Welfare and Sports, hip fracture associated crude total costs in 2017 in the Netherlands were 460.9 million euro[50]. Economic evaluation of healthcare costs is important as the burden of healthcare costs threatens to exceed the financial resources available.

CHALLENGES FOR THE MANAGEMENT OF HIP FRACTURE PATIENTS AND RESEARCH QUESTIONS

The ageing of society in combination with increase in older patients with major comorbidities will increase disability rate of hip fracture patients and will be a major challenge for the healthcare system as well as for society. In vulnerable patients after a hip fracture it raise the following questions to improve the clinical management:

- What are the differences in mortality, QoL, functional outcome and costs between nonoperative (NOM) and operative management (OM) of hip fractures in patients above 65 years?
- Which are the best predictor variables for 30-day and for 1-year mortality in patients above 65 years with a hip fracture?
- Which factors influencing the decision-making of treatment for hip fractures in frail patients?
- What is the effect of frailty on QoL in patients after hip fracture?
- What is the prevalence and what are prognostic factors of psychological distress in patients with a hip fracture?
- What is the impact for informal caregivers of providing informal care to patients after hip fracture?
- What is the burden of illness of hip fractures in the Netherlands?

The aims of this thesis are based on these questions (Figure 4).

AIMS AND OUTLINE OF THIS THESIS

The aims of this thesis are operationalized according to the following objectives, divided in three parts:

I. To reveal risk profiles and factors for poor outcome in patients after hip fracture to support clinicians, patients and families in tailoring treatment for medical decision-making.
II. To describe prognostic factors of QoL and psychological distress in patients after hip fracture.
III. To investigate the societal impact of hip fractures in patients with respect to informal care and the burden of illness.

Figure 4. The aims of this thesis visualized in keywords

In **part I**, we reveal risk profiles and factors for poor outcome in patients with a hip fracture to support clinicians, patients and relatives in tailoring treatment for medical decision-making. In **chapter 2**, we perform a systematic review and meta-analysis of the literature to provide an overview of differences in mortality, (HR)QoL, functional outcome, and costs between OM and NOM of hip fractures in patients above 65 years. **Chapter 3** presents two easy to use clinical prediction models for 30-day and 1-year mortality after hip fracture in patients of 65 years in older. In **chapter 4** we identify factors in various stakeholders involved in hip fracture care that could influence the decision to recommend OM or NOM in frail older patients with a hip fracture. We create a decision-support tool to identify patients potentially eligible to discuss NOM, by using data from the BIOS.

In **part II**, we present the results of the BIOS and describe prognostic factors of QoL and psychological distress in patients after hip fracture. In **chapter 5** we examine the effect of frailty on HS and QoL following one year after hip fracture.

In c**hapter 6** we determine the prevalence and prognostic factors for psychological distress, including symptoms of depression, symptoms of anxiety and symptoms of PTS, in patients during one year after hip fracture.

In **part III**, we describe from results of the BIOS the societal impact of hip fractures with respect to informal care and the burden of illness. **Chapter 7** determines the nature, intensity and the care-related Quality of Life (CarerQoL) of informal caregivers of hip-fractured patients in the first 6 months. **Chapter 8** determines the burden of illness of hip fractures in older Dutch patients for specific time periods after surgery.

Chapter 9 provides the summary with the main findings of this thesis. **Chapter 10** provides the general discussion with recommendations for future research.

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PART I

Medical decision-making

CHAPTER 2

Hip fractures in elderly people: Surgery or no surgery? A systematic review and meta-analysis

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Geriatric orthopaedic surgery & rehabilitation. 2017; 8(3), 173-180.

ABSTRACT

Introduction: Increasing numbers of patients with hip fractures also have advanced comorbidities. A majority are treated surgically. However, a significantly increasing percentage of medically unfit patients with unacceptably high risk of perioperative death are treated non-operatively. Important questions about patients' pre-fracture quality of life (QoL) and future perspectives should be asked before considering different treatment options to assess what kind of treatment is advisable in frail elderly high-risk patients with a hip fracture.

Objective: The aim of this review was to provide an overview of differences in mortality, health-related QoL [(HR)QoL], functional outcome and costs between nonoperative management (NOM) and operative management (OM) of hip fractures in patients above 65 years.

Methods: A systematic literature search was performed in EMBASE, OvidSP, PubMed, Cochrane Central and Web of Science for observational studies and trials. Observational studies and randomized controlled trials comparing NOM with OM in hip fracture patients were selected. The methodological quality of the selected studies was assessed according to the Methodological Index for Nonrandomized Studies (MINORS) or Furlan checklist.

Results: Seven observational studies were included with a total of 1189 patients, of 242 whom (20.3%) were treated conservatively. The methodological quality of the studies was moderate (mean 14.7, standard deviation (SD): 1.5). The 30-day and 1-year mortality were higher in the non-operative group (odds ratio (OR): 3.95, 95% confidence interval (CI): 1.43-10.96; OR 3.84, 95% CI 1.57-9.41). None of the included studies compared QoL, functional outcome or health-care costs between the two groups.

Conclusion: This systematic review and meta-analysis demonstrated that only a few studies with small number of patients comparing NOM with OM were published. A significantly higher 30-day and 1-year mortality was revealed in non-operatively treated hip fracture patients. No data were found examining (HR)QoL and costs. Further work is needed to enable shared decision-making and to initiate NOM in frail elderly patients with advanced comorbidity and limited life expectancy.

Keywords: Hip fracture – (non) operative treatment – elderly – mortality – quality of life

INTRODUCTION

Early surgical repair has been shown to give the best outcomes in frail elderly patients with a hip fracture. With a 30-day mortality rate of 10 to 13 percent and a 1-year mortality rate ranging from 22% to 33%, there may be some patients who are at the end of life and would be better served with non-operative management (NOM)[1,2].

Randomized controlled trials (RCTs) on the effectiveness of surgical treatment are scarce, due to ethical issues. In 2008 Handoll et al. published a Cochrane systematic review comparing conservative with operative treatment for hip fractures[3]. They reported insufficient evidence with potentially serious bias to prove that operative management (OM) is better than bedrest and traction. In addition to mortality, other outcomes with major impact for elderly patients with a hip fracture are functional outcome, (health related) quality of life [(HR)QoL], and health status[4,5]. The importance of these factors on determination of OM or NOM is unknown.

The aim of this systematic review was to provide an overview and update of the literature comparing NOM with OM for hip fractures in people older than 65 years. To obtain an overview of outcome measures, we searched for mortality, (HR) QoL, functional outcome and health-care costs. We also attempted to examine the relationship of comorbidities to decision for OM or NOM within these studies.

MATERIALS AND METHODS

Search strategy

A systematic literature search was conducted for hip fractures and treatment in EMBASE, OvidSP, PubMed, Cochrane Central and Web-of-Science from 1966 up to May 2015. In addition, references of all retrieved articles were screened for eligible studies that were not found in the initial search.

The literature search included keywords related to 'proximal femoral fracture', 'elderly', 'surgery', 'conservative treatment', 'mortality', 'comorbidity', 'quality of life', 'function' and 'costs'. The search strategy is outlined in supplemental file.

Study selection

Studies comparing NOM with OM in hip-fracture patients were selected. The following inclusion and exclusion criteria were used to determine eligibility of a study: (i) Elderly patients (age ≥65 years) who sustained a hip fracture; (ii) Hip fractures were defined as femoral neck, pertrochanteric, intertrochanteric or subtrochanteric fractures. Greater trochanteric fractures, isolated lesser trochanteric fractures, acetabular fractures and pelvic fractures were excluded; (iii) The main outcome measure was 30-day and/or 1-year mortality; (iv) The study was published in a peer-reviewed English-language journal; (v). A full text of the article was available. Studies that only included mechanically stable (femoral neck Garden 1) fractures were excluded. Also case reports, comments, editorials, guidelines, meta-analyses, and reviews were excluded.

Data collection

Two reviewers (CLPvdR and MACdJ) independently selected potentially relevant studies based on title, abstract, and full text of the studies retrieved in the literature search. Discrepancies in selection between the two reviewers were resolved by consensus. In case of persistent disagreement, a third reviewer (TG) was consulted. The search procedure was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram[6]. Eligibility criteria were reported in accordance with Participants, Intervention, Comparison, Outcome, and Study design. The following study characteristics were extracted from the included studies: first author, year of publication, country, design, year of inclusion, sample size, type of fracture, type of NOM and OM, mean age, gender, and length of follow up. In case of absence of one of these characteristics, the corresponding author was contacted. Outcome measures such as mortality, (HR)QoL, function and costs were reported. Other outcomes of the included studies were described as present or not: pain, causes of death, complications, residential status, length of stay, comorbidity, and American Society of Anesthesiologists (ASA) classification.

Quality assessment

The quality of the included studies was independently assessed by two reviewers (CLPvdR and MACdJ). Disagreements were resolved by consensus. For RCTs we used the 12 risk-of-bias criteria of Furlan et al[7]. Each item was scored as 'yes', 'no' or 'unsure'. For observational or nonrandomized surgical studies, we used the 12-item Methodological Index for Nonrandomized Studies (MINORS)[8]. MINORS is a valid instrument and designed to assess the methodological quality

of nonrandomized surgical studies, whether comparative or noncomparative. Each item was scored a '0' (not reported), '1' (not adequately reported) or '2' (adequately reported). The maximum score was 24 for comparative studies. MINORS was not converted to a degree of bias by the authors.

Data and statistical analysis

We included all eligible articles and performed a meta-analysis of mortality in hip fracture patients. The 30-day and 1-year mortality rates were extracted from the studies and included in the meta-analysis. Effect measures of interest were crude and pooled odds ratio (OR) and corresponding 95% confidence interval (CI). The p-value was based on a 2-sided test and was considered statistically significant at $p<0.05$. Heterogeneity between the studies was determined using I^2 [9]. Interpretation of I^2 of 30% to 60% may represent moderate heterogeneity, and substantial heterogeneity was defined as $I^2 \geq 60$ [10]. The random-effects model was used to calculate the pooled OR (95% CI), due to heterogeneity between cohorts. Analyses were performed with Review manager (Revman) version 5.3 [11].

RESULTS

Search results

A total of 1481 studies were found (815 from EMBASE, 437 from OvidSP, 3 from PubMed, 11 from Cochrane Central and 215 from Web-of-Science). After removal of duplicate articles (n=487), 994 unique titles and abstracts were screened for eligibility. Finally, 7 articles fulfilled the inclusion criteria. The most common reasons for exclusion were the absence of a comparison between NOM and OM and a population aged under 65 years. The flow diagram of the study is shown in figure 1.

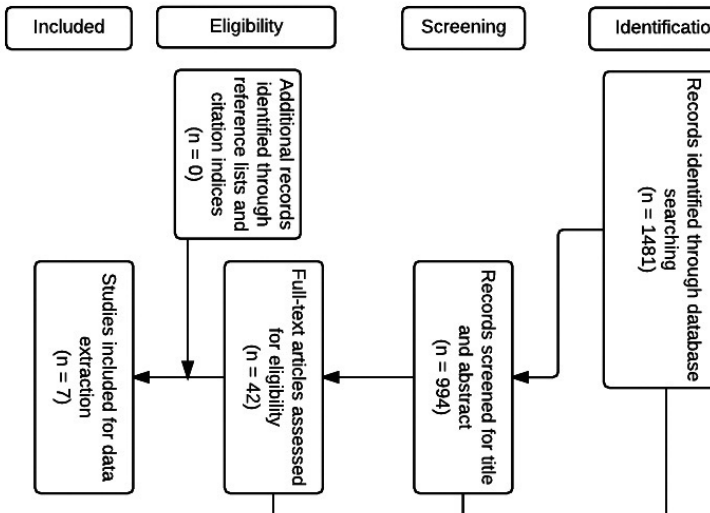

Figure 1. Flow diagram; selection of articles: operative vs. non-operative management in elderly patients with a hip fracture

Study characteristics

The included observational studies were published between 2001 and 2013. In five studies, the data were retrospectively gathered[12-16]. The mean follow up was 11.3 months (range: 1-24 months). Sample sizes ranged from n=23 [16] to n=666 [13]. A total of 1189 patients were included, 242 (20.3%) of whom were treated conservatively. The mean age ranged from 76.9 [14] to 101.8 [16] years. Five studies included intracapsular and extracapsular fractures and made no distinction between mechanically stable and unstable femoral neck fractures[12,14-17]. Two studies published only about displaced femoral neck fractures[13,18]. Table 1 demonstrates the characteristics of all included studies and table 2 presents an overview of the outcome measures.

Table 1. Overview of included studies comparing operative versus non-operative management

Study, year of publication	Setting	Design	Prospective	Year	Study population (number; years)	Type of fracture	NOM [a]	OM[b]	Mean age	% Female	FU[c] months
Beloosesky et al. 2001 [12]	Israel	Cohort	No	1993 -1999	N=78; >65y	intracapsular (47.4%) extra-capsular (46.2%) subtrochanteric (6.4%)	N=64 82.1% EM[i] (even in bedridden patients)	N=14 17.9% IF [d]; HA[e]	♂ 81.2 ♀ 82.0 (65-98)	65.4	12
Dedovic et al. 2013 [17]	Bosnia and Herze-govina	Non-RCT[j]	R-P	2011 -2012	N=66; >65y *High cardiac risk*	femoral neck (27.3%) intertrochanteric (53.0%) subtrochanteric (19.7%)	N=32 48.5% unknown	N=34 51.5% unknown	78.5 (±5.46; 65-92)	NOM:75 OM:67.6	6
Gregory et al. 2010 [18]	United Kingdom	Non-RCT	Yes	2005-2006	N=102; >70y	displaced femoral neck	N=22 21.6% EM	N=80 78.4% uncemented Austin Moore HA	84	66.7	12
Ishimaru et al. 2012 [13]	Japan	Cohort	No	2001 -2009	N=666; >70y	displaced femoral neck (42.6%) ≥ type 2 trochan-teric (57.4%)	N=20 3.0% traction	N=646 97% IF; HA	NOM: 83.7 OM: 85.4	NOM:95 OM:81.6	12

Table 1. Continued.

Study, year of publication	Setting	Design	Prospec-tive	Year	Study population (number; years)	Type of fracture	NOM [a]	OM[b]	Mean age	% Female	FU[c] months
Jain et al. 2003 [14]	Canada	Case control	No	1989 - 1995	N=170; >65y	femoral neck (50%) intertrochanteric (50%)	N=62 36.5% -BR[k]: n=41 -EM: n= 21	N=108 63.5% IF; HA; THA[i]	BR: 76.9 (17.0) EM: 78.8 (10.8) OM: 79.1 (13.2)	NOM: 64.5 OM: 63.9	1
Ooi et al. 2005 [15]	Singa-pore	Cohort	No	1998 -1999	N=84; >90y	femoral neck (56.0%) intertrochanteric (44.0%)	N=38 45.2% Hamilton -Russell traction	N=46 54.8% HA; DHS[f]; PFN[g]; B-HA[h]	-	86.9	24
Shabat et al. 2004 [16]	Israel	Cohort	No	1990 -2001	N=23; >100y	femoral neck (17.3%) pertrochanteric (82.7%)	N=4 17.4% BR with skin trac-tion	N=19 82.6% DHS; Thompson HA	101.8	73.9	12

List of abbreviations: [a] NOM: non-operative management; [b] OM: operative management; [c] FU: follow up; [d] IF: internal fixation; [e] HA: hemiarthroplasty; [f] DHS: dynamic hip screw; [g] PFN: proximal femoral nail;[h] B-HA: bipolar hemiarthroplasty; [i] THA: total hip arthroplasty; [j] RCT: randomized controlled trial; [k] BR: bedrest; [l] EM: early mobilization

Table 2. Outcome measures of the included studies

Study	Mortality	Comor-bidity	(HR) QOL	Function and mobility	Costs	Pain	Causes of death	ASA	Compli-cations	Resi-dential status	Length of stay
Beloosesky et al.[12]	+ [c]	+	-	+	-	-	-	+	+	+	+
Dedovic et al.[17]	+ [a,b]	+	-	-	-	-	-	-	-	-	-
Gregoryet al.[18]	+ [a,c]	+	-	+	-	-	+	+	+	+	+
Ishimaru et al.[13]	+ [c]	+	-	-	-	-	+	+	+	-	-
Jain et al.[14]	+ [a]	+	-	-	-	-	-	+	+	-	+
Ooi et al.[15]	+ [a,b,c,d]	+	-	+	-	-	+	+	+	-	+
Shabat et al.[16]	+ [a,c]	+	-	+	-	-	-	+	+	+	+

[a] 30 day; [b] 6 months; [c] 1 year; [d] 2 years

Outcome measures: +: present or –: lacking

Table 3. Quality assessment of the included studies

MINORS		Beloos-esky[12]	Dedovic[17]	Gregory[18]	Ishi-maru[13]	Jain[14]	Ooi[15]	Shabat[16]
1	A clearly stated aim	2	1	0	2	2	2	2
2	Inclusion of consecutive patients	2	2	2	2	2	2	2
3	Prospective collection of data	1	1	2	0	0	0	0
4	Endpoints appropriate to the aim of the study	2	2	1	2	2	2	2
5	Unbiased assessment of the study endpoint	0	0	0	0	0	0	0
6	Follow-up period appropriate to the aim of the study	1	1	2	2	1	2	2
7	Loss to follow up less than 5%	1	0	2	1	2	2	2
8	Prospective calculation of the study size	0	0	0	0	0	0	0
9	An adequate control group	2	2	2	2	2	2	2
10	Contemporary groups	2	2	2	2	2	2	2
11	Baseline equivalence of groups	1	1	1	1	2	0	0
12	Adequate statistical analyses	1	0	1	1	2	1	0
Total		15	12	15	15	17	15	14

Abbreviation: MINORS: Methodological Index for Nonrandomized Studies

Quality assessment

The mean MINORS score for the included observational studies was 14.7 (standard deviation (SD): 1.5; table 3). One study used prospectively collected data and these were adequately reported[18]. None of the studies reported about blinding evaluation for unbiased assessment. All studies had an adequate control group, because OM is recognized as the optimal intervention in case of hip fractures. Jain et al.[14] reported adequate baseline equivalence of the two groups, NOM and OM. They also presented an adequate measure of effect with an OR (95% CI).

Meta-analysis: mortality

Thirty-day mortality was reported in 5 studies[14-18] and 1-year mortality was reported in four studies[13,15,16,18] for both treatment groups. Beloosesky et al.[12] reported a 1-year mortality percentage of 32% without a significant difference between OM and NOM. This author was contacted by email, but did not respond to the request of sending the mortality rates for both groups.

The forest plots of the meta-analyses of 30-day and 1-year mortality comparing NOM and OM are shown in figures 2 and 3. The plots show moderate degree of heterogeneity of effects in the observational studies. The unadjusted pooled OR of 30-day mortality revealed a 3.95-fold higher mortality for NOM than for OM (95% CI: 1.43-10.96). For 1-year mortality an unadjusted pooled OR of 3.84-fold higher mortality for NOM was calculated (95% CI: 1.57-9.41).

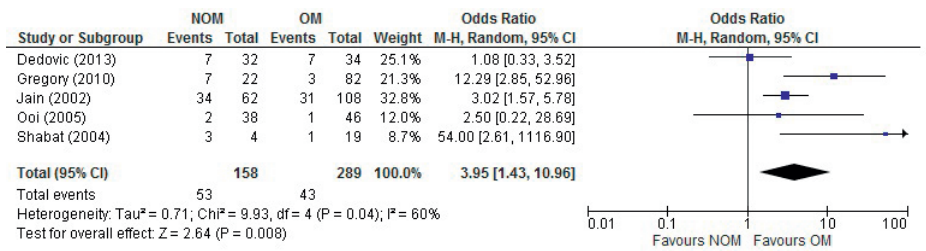

Figure 2. 30-day mortality

Bedrest in conservatively treated patients revealed a 3.8-fold higher 30-day mortality (95% CI: 1.1-14.0) than early mobilization[14]. Dedovic et al. reported a 6-month mortality and we calculated an unadjusted pooled OR of death associated with NOM to OM, which was 1.09 (95% CI: 0.33-3.52). The calculated unadjusted pooled OR for 2-year mortality given by Ooi et al. resulted in 1.95 (95% CI: 0.82-4.67). We also calculated the unadjusted pooled OR for 1-year mortality in three studies (i.e. Gregory et al., Ooi et al., Shabat et al.) in which patients survived beyond 30 days, which was 1.57 (95% CI: 0.77-3.20).

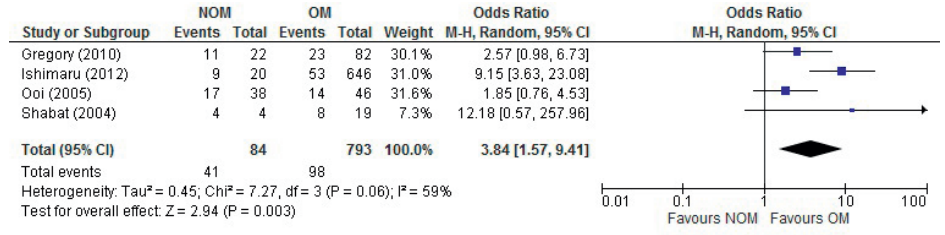

Figure 3. 1-year mortality

Quality of Life

None of the articles reported (HR)QoL after NOM or OM.

Function and mobility

Two studies used the Katz Index of Activities of Daily Living to assess functional status as a measurement of the patient's ability to perform basic activities of daily living (BADL) independently without comparing NOM to OM[12,16]. Beloosesky et al. discovered no significant difference in survival between prefracture independent versus partially and completely dependent patients. Shabat et al. did not distinguish between OM and NOM in their population of patient ages 100 and older. Sixteen patients had not been able to perform any of the BADL pre-fracture, whereas 7 patients had only been partially able to perform their BADL. After the hip fracture three of these patients had a slight reduction in the BADL and four were unable to do BADL. Among 19 of 23 operated patients, 11 had ambulated with a walker prior to the fracture and 8 patients had been nonambulatory. Of the 11 patients, only 4 patients regained their walking ability with a walker and 7 became nonambulatory. In the conservatively treated group (n=4), two patients had been able to walk prior to the fracture and all of them could not anymore walk after the fracture. One study distinguished between independent and dependent ambulators and found that OM significantly increased the ability for independent ambulation in patients which were independent prior to fracture ($p<0.01$)[15]. Gregory et al.[18] only analyzed mobility in 11 survivors of NOM at 1-year follow-up without using an adequate measuring instrument.

Costs

None of these studies reported on the direct or indirect medical costs.

Table 4. Comorbidity reported in included studies

Study		Beloosesky [12] (N; %)	Dedovic[17,a] (N; %)	Gregory[18,b] (N; %)	Ishimaru[13] (N; %)	Jain[14] (N; %)	Ooi[15,c] (N; %)	Shabat[16] (N; %)
Dementia	NOM	38 (48.8)[d]		3 (13.6)	10 (50.0)	22 (35.5)	46 (54.8)[d]	15 (65.2)
	OM				247 (38.2)	28 (25.9)		
Ischemic heart disease / chronic heart failure	NOM	67 (85.9)[d]	31 (96.9)	11 (50.0)	12 (60.0)	19 (30.6)		8 (34.8)
	OM		31 (91.2)		158 (24.5)	44 (40.7)		
CVA/TIA	NOM		12 (37.5)	6 (27.3)	6 (30.0)	8 (12.9)		
	OM		16 (47.1)		91 (14.1)	24 (22.2)		
DM	NOM	20 (25.6)[d]	20 (62.5)	6 (27.3)	3 (15.0)	5 (8.1)		10 (43.5)
	OM		22 (64.7)		86 (13.3)	14 (13.0)		
COPD/Asthma	NOM	16 (20.5)[d]		3 (13.6)	3 (15.0)	15 (24.2)		
	OM				44 (6.8)	32 (29.6)		
Renal insufficiency	NOM	11 (14.1)[d]	6 (18.8)		5 (25.0)	7 (11.3)		
	OM		1 (2.9)		31 (4.8)	9 (8.3)		
Malignancy	NOM	5 (6.4)[d]		4 (18.2)	4 (20.0)	14 (22.6)		
	OM				60 (9.3)	9 (8.3)		
ASA I/II	NOM	33 (51.6)		1 (4.5)	2 (10.0)	3 (4.8)	62 (73.8)[d]	
	OM	13 (92.9)		30 (37.5)	385 (59.6)	4 (3.7)		
ASA III/IV	NOM	31 (48.4)		21 (95.5)	18 (90.0)	59 (95.2)	22 (26.2)[d]	
	OM	1 (7.1)		50 (62.5)	261 (40.4)	104 (96.3)		

List of abbreviations: N: number of patients; NOM: non-operative management; OM: operative management

[a] Only inclusion of patient's with three or more cardiac comorbid risk factors: chronic heart failure, previous myocardial infarction or angina pectoris, insulin dependent diabetes mellitus, previous cerebrovascular insult or transitory ischemic attack and renal insufficiency.

[b] Only report for 22 non-operatively treated patients

[c] Only report about dementia

[d] Total reported numbers for NOM and OM

Comorbidity

The most prevalent comorbidities were dementia, cardiac diseases, and diabetes mellitus (table 4). ASA classification was given in six articles. None of these studies involved patients with ASA grade V. The main causes of surgical delay and unstable medical conditions described by Beloosesky et al. were cardiac problems (38,5%), infections (37,2%) and diabetic or electrolyte abnormalities (12.8%).

Three studies[12,13,18] reported higher overall ASA grades in nonoperatively treated patients. Jain et al.[14] described a significantly higher number of patients with ASA IV grade in the bedrest group compared to the early mobilization group (p=0.0004). Preadmission comorbidities of both groups were similar, except for depression, which was more frequent in the early mobilization group. Ishimaru et al.[13] showed that heart disease was significantly more common in nonoperatively treated patients than in operatively treated patients (p<.01). Dedovic et al.[17] only reported about elderly patients with high cardiac risk (≥ 3 risk factors), based on the Lee index. Ooi et al.[15] reported that at least 62 of 84 patients had one or more diseases in terms of comorbidity. In patients with a mini-mental test score of less than severn, the probability of death over the subsequent 24 months was significantly increased (p<0.05).

Shabat et al.[16] showed no significant difference in the number of major background diseases between NOM and OM (2.74 ± 1.01 vs. 2.75 ± 0.83; p>0.05). The operatively treated group of patients with a 1-year survival had on average 2.0 ± 0.77 background diseases (survival less than 1 year: 3.75 ± 0.46; p < 0.0001). In five studies, patients who were medically unfit due to comorbidity were treated nonoperatively[12-15,18].

DISCUSSION

This review and meta-analysis aimed to provide an overview of studies comparing nonoperative with operative treatment with respect to mortality, (HR)QoL, and costs in elderly patients with a hip fracture.

In general, 30-day and 1-year mortality were higher in the nonoperatively treated group. None of the included studies compared outcome measures of (HR)QoL, functional outcome or health-care costs between OM and NOM.

This review included 7 nonrandomized and observational studies of moderate quality according to MINORS. The meta-analysis revealed that the unadjusted pooled 30-day and 1-year mortality ORs were almost 4 times higher for NOM compared to OM.

No RCTs have been performed since the previous Cochrane review of adults with a hip fracture. Handoll et al. included five randomized trials, which were two abstracts and one unpublished study[3,19-22]. Those studies were published between 1975 and 1994 and the authors did not report on (HR)QoL in these populations. Our review included studies that were published between 2001 and 2013 and we focused on frail elderly patients of 65 years and older in our systematic review. However, none of the studies that compared NOM with OM used a frailty measure. Therefore, we tried to assess the severity of the patients' health problems at time of admission, by describing comorbidity and ASA classification as represented in the included studies.

There are some limitations of our study. First, the reported ORs could not be adjusted for potential confounders, such as comorbidity, gender, age, mental health status, degree of frailty or type of intervention. These unadjusted pooled ORs should be interpreted with caution. Von Hippel et al. showed that I^2 should be presented and interpreted with caution in small meta-analyses[23]. Therefore, the heterogeneity we found may be considered as imprecise and biased. The random-effects model was used because the effect size varied from study to study and this model was more likely to fit the actual sampling distribution[24]. The effect size might be higher or lower due to differences in case mix.

Second, due to missing information about types of intracapsular fractures we could not distinguish between mechanically stable and unstable fractures[12,14-17]. We excluded all studies selectively reported Garden 1 femoral neck fractures, as these are fundamentally different from displaced fractures and may be treated with NOM[25]. Finally, this study is not generalizable to countries where surgery may not be an option for every patient with a hip fracture.

Future research on differences in outcome between NOM and OM should measure the pre- and post-fracture status in elderly patients using instruments for frailty and (HR)QoL (e.g. European Quality of Life-5 Dimensions[26], ICEpop CAPability measure for Older people[27-29], Groningen Frailty Indicator[30]) with short and long-term follow-up. Cost-effectiveness is also important, including direct

and indirect medical costs with calculation of Quality-adjusted life years (QALYs). The optimal study design to overcome selection bias is an RCT. However, such a study design would lead to several ethical issues because clinicians would be faced with performing surgery on patients with a high risk to die perioperatively or with withholding surgery from patients who are very likely to benefit from an operation. Future research could help clinicians to determine which category of patients could be treated conservatively by developing risk profiles and, for example, a risk score chart.

In conclusion, this systematic review and meta-analysis demonstrated that only a few observational studies with a small number of patients comparing NOM with OM have been published. A significantly higher 30-day and 1-year mortality was revealed in nonoperatively treated hip fracture patients above 65 years compared to operatively treated patients. Comorbidity did not seem to purely drive this decision-making. No data was found examining (HR)QoL, degree of frailty and costs. Future studies are urgently needed to provide this important information to aid patients and providers in decision- making for surgical repair, particularly in frail elderly patients.

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Supplemental file. Search strategy 27 may 2015

Database	Total	Deduplicated
Embase.com (Embase, Medline)	815	806
Medline (OVID)	437	122
PubMed supplied by publisher	3	1
Cochrane Central	11	1
Web of Science	215	64
Total	**1481**	**994**

Embase (Embase, Medline) 815 (806)

('hip fracture'/exp OR ((hip OR femor* OR femur* OR collum* OR trochant* OR subtroch* OR intertroch* OR pertroch*) NEAR/3 fractur*):ab,ti) AND ('aged'/exp OR 'geriatric patient'/de OR 'geriatrics'/de OR 'elderly care'/exp OR 'geriatric hospital'/de OR 'geriatric rehabilitation'/de OR ((aged OR old* OR elder*):ab,ti NOT (child/exp OR adolescent/de OR (child* OR adolescen* OR teen* OR youth*):ab,ti)) OR (senior* OR geriatr* OR psychogeriatr* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*):ab,ti) AND ('surgery'/exp OR (surg* OR operat* OR orthop* OR fixat* OR arthroplast* OR hemiarthroplast* OR prosthe* OR replac* OR Girdlestone OR screw*):ab,ti) AND ('conservative treatment'/exp OR (conservat* OR nonsurg* OR nonoperativ* OR (non NEXT/1 (operat* OR surg*)) OR traction* OR bedrest OR (bed NEXT/1 rest*) OR (watch* NEAR/3 wait*)):ab,ti) AND ('treatment outcome'/exp OR 'mortality'/exp OR 'morbidity'/de OR 'quality of life'/exp OR 'cost benefit analysis'/de OR 'health status'/exp OR ((qualit* NEAR/3 (life OR living)) OR QALY OR QOL OR outcome* OR mortalit* OR death* OR morbid* OR failure* OR fitness* OR function* OR mobilit* OR cost* OR ASA):ab,ti)

Ovid SP (Medline) 437 (122)

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((hip[tiab] OR femor*[tiab] OR femur*[tiab] OR collum*[tiab] OR trochant*[tiab] OR subtroch*[tiab] OR intertroch*[tiab] OR pertroch*[tiab]) AND fractur*[tiab]) AND (((aged[tiab] OR old*[tiab] OR elder*[tiab]) NOT (child*[tiab] OR adolescen*[tiab] OR teen*[tiab] OR youth*[tiab])) OR senior*[tiab] OR geriatr*[tiab] OR psychogeriatr*[tiab] OR septuagenarian*[tiab] OR octogenarian*[tiab] OR nonagenarian*[tiab] OR centenarian*[tiab] OR supercentenarian*[tiab]) AND (surger*[tiab] OR surgic*[tiab] OR operation*[tiab] OR operative*[tiab] OR orthop*[tiab] OR fixat*[tiab] OR arthroplast*[tiab] OR hemiarthroplast*[tiab] OR prosthe*[tiab] OR replac*[tiab] OR Girdlestone[tiab] OR screw*[tiab]) AND (conservat*[tiab] OR nonsurg*[tiab] OR nonoperativ*[tiab] OR non operat*[tiab] OR non surg*[tiab] OR traction*[tiab] OR bedrest[tiab] OR bed rest*[tiab] OR (watch*[tiab] AND wait*[tiab])) AND ((qualit*[tiab] AND (life[tiab] OR living[tiab])) OR QALY[tiab] OR QOL[tiab] OR outcome*[tiab] OR mortalit*[tiab] OR death*[tiab] OR morbid*[tiab] OR failur*[tiab] OR fitness*[tiab] OR functional*[tiab] OR function[tiab] OR functions[tiab] OR functioning[tiab] OR mobilit*[tiab] OR cost[tiab] OR costs[tiab] OR ASA[tiab]) *AND publisher[sb]*

Cochrane Central 11 (0)

(((hip OR femor* OR femur* OR collum* OR trochant* OR subtroch* OR intertroch* OR pertroch*) NEAR/3 fractur*):ab,ti) AND (((aged OR old* OR elder*):ab,ti NOT ((child* OR adolescen* OR teen* OR youth*):ab,ti)) OR (senior* OR geriatr* OR psychogeriatr* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*):ab,ti) AND ((surg* OR operat* OR orthop* OR fixat* OR arthroplast* OR hemiarthroplast* OR prosthe* OR replac* OR Girdlestone OR screw*):ab,ti) AND ((conservat* OR nonsurg* OR nonoperativ* OR (non NEXT/1 (operat* OR surg*)) OR traction* OR bedrest OR (bed NEXT/1 rest*) OR (watch* NEAR/3 wait*)):ab,ti) AND (((qualit* NEAR/3 (life OR living)) OR QALY OR QOL OR outcome* OR mortalit* OR death* OR morbid* OR failure* OR fitness* OR function* OR mobilit* OR cost* OR ASA):ab,ti)

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TS=((((hip OR femor* OR femur* OR collum* OR trochant* OR subtroch* OR intertroch* OR pertroch*) NEAR/3 fractur*)) AND (((aged OR old* OR elder*) NOT ((child* OR adolescen* OR teen* OR youth*))) OR (senior* OR geriatr* OR psychogeriatr* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*)) AND ((surg* OR operat* OR orthop* OR fixat* OR arthroplast* OR hemiarthroplast* OR prosthe* OR replac* OR Girdlestone OR screw*)) AND ((conservat* OR nonsurg* OR nonoperativ* OR (non NEXT/1 (operat* OR surg*)) OR traction* OR bedrest OR (bed NEXT/1 rest*) OR (watch* NEAR/3 wait*))) AND (((qualit* NEAR/3 (life OR living)) OR QALY OR QOL OR outcome* OR mortalit* OR death* OR morbid* OR failure* OR fitness* OR function* OR mobilit* OR cost* OR ASA)))

CHAPTER 3

Development and validation of the Brabant Hip Fracture Score for 30-day and 1-year mortality

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ABSTRACT

Introduction: Hip fractures in the elderly are associated with advanced comorbidities and high mortality rates. Mortality prediction models can support clinicians in tailoring treatment for medical decision making in frail elderly patients. The aim of this study was to develop and internally validate the Brabant Hip Fracture Score, for 30-day (BHFS-30) and 1-year mortality (BHFS-365) after hip fracture.

Material and methods: A cohort study was conducted in two hospitals in operatively treated patients of 65 years and older with a hip fracture. Manual backward multivariable logistic regression was used to select independent predictors of 30-day and 1-year mortality. Internal validation was performed using bootstrapping techniques. Model performance was assessed with: (i) discrimination via the area under the receiver operating characteristic curve (AUC); (ii) explained variance via Nagelkerke's R^2; (iii) calibration via Hosmer-Lemeshow (H&L) test and calibration plots.

Results: Independent predictors of 30-day mortality were: age, gender, living in an institution, Hb, respiratory disease, diabetes and malignancy. In addition, cognitive frailty and renal insufficiency, were selected in the BHFS-365. Both models showed acceptable discrimination after internal validation (AUC=0.71 & 0.75). The Hosmer-Lemeshow test indicated no lack of fit ($p>0.05$).

Conclusion: We demonstrated that the internally validated and easy to use BHFS in surgically treated elderly patients after a hip fracture showed acceptable discrimination and adequate calibration. In clinical practice a cutoff of BHFS-30 ≥24 could identify frail elderly patients at high risk for early mortality and could support clinicians, patients and families in tailoring treatment for medical decision making.

Keywords: clinical prediction model, mortality, hip fracture, elderly

INTRODUCTION

Hip fractures are a socioeconomic burden to both individual and the community, and result in loss of independence, reduced quality of life and substantial mortality[1,2]. Outcomes are worse in extremely elderly and nursing home residents, with a 120-day mortality of 38.1%[3,4]. Specifically, in this frail and medically unfit patients with advanced comorbidities, the decision to pursue life-prolonging surgery needs to be carefully considered in the context of patient's life expectancy[5,6].

Clinical prediction models provide insight into the relative effects of predictors for prognosis of mortality. These models provide absolute risk estimates for individual patients in order to optimize quality of care.

Several clinical prediction models for mortality following hip fracture surgery have been published[7,8]. The most promising one for predicting 30-day mortality, the Nottingham Hip Fracture Score (NHFS) and the Almelo Hip Fracture Score (AHFS), demonstrated a reasonable discrimination[9-11]. The NHFS consisted of seven variables: age, gender, pre-fracture institutionalization, mini-mental state examination (MMSE), admission serum hemoglobin (Hb), number of comorbidities and malignancy. The AHFS modified the NHFS and added two predictor variables: American Society of Anesthesiologists (ASA) grading and Parker mobility score.

However, these clinical prediction models have limited discriminative power, used suboptimal or no form of internal validation, and used some difficult variables to obtain, such as MMSE[8,12]. Moreover, there is still debate about appropriate cut-off points to identify patients at high risk of mortality following a hip fracture and this should be clarified before a prediction model could be adopted into routine practice.

The primary objective of this study was to develop and internally validate two easy to use clinical prediction models: the Brabant Hip Fracture Score (BHFS), with a combination of best predictor variables for 30-day mortality (BHFS-30), and for 1-year mortality (BHFS-365), in patients above 65 years with a hip fracture. These models could contribute to evidence-based input for medical decision making and could be useful in frail elderly patients considering operative or nonoperative management[13,14]. According to the Transparent Reporting of multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)

statement for the BHFS were assessed[15]: (i) evaluation of model performance; (ii) internal validation and (iii) risk model presentation.

MATERIAL AND METHODS

Study design and population

A retrospective cohort study was conducted to develop the BHFS. Data were obtained from two Dutch hospitals: Elisabeth-TweeSteden Hospital, Tilburg and Catharina Hospital, Eindhoven. Patients aged 65 years and older with a hip fracture admitted to Elisabeth-TweeSteden Hospital from January 2010 to December 2013 and admitted to Catharina Hospital from January 2009 and December 2011 were included. The following exclusion criteria were used: (i) patients treated with non-operative treatment (ii); isolated greater trochanteric fractures, acetabular fractures and pelvic fractures; (iii) pathological fractures; (iv) periprosthetic hip fractures and (v) patients with a metachronous hip fracture at the contralateral site in the inclusion period. Operative treatment was according to current guidelines. Intracapsular hip fractures were treated with hemi- or total hip arthroplasty, cannulated screws or dynamic hip screw (DHS). Extracapsular fractures were treated with DHS or intramedullary nailing.

Measures

Outcome – Two outcomes were modeled: 30-day mortality (BHFS-30) and 1-year mortality (BHFS-365) in patients with a hip fracture. Thirty-day and 1-year mortality, defined as death within 30 days or 1 year after operative treatment, were collected from Safe Communication in Healthcare (VECOZO)[16].

Predictors – Predictor variables were collected from the Dutch Trauma Registry and from medical history in electronic medical records. The following predictor variables were selected from a systematic review published by Hu *et al.*[17]: age[18-22], gender[18,21,23-25], pre-fracture residence[25,26], Hb[27-29], pre-fracture mobility[19,21,24,25], fracture type[24] and ASA grading[18,21,26,30].

Comorbidities were selected such as respiratory disease[25,31], cardiovascular disease[20,21,30], cerebrovascular disease[32,33], diabetes[21,24,32], renal insufficiency[25,34,35], depression[36] and malignancy[21,25,30]. Respiratory disease consists of chronic respiratory conditions, such as asthma or chronic obstructive pulmonary disease (COPD). Cardiovascular disease including previous ischemic heart disease, cardiac arrhythmia or valvular heart disease. Cerebrovascular disease consisted

of a stroke or a transient ischemic attack. Renal insufficiency was determined by estimated glomerular filtration rates (eGFR) of less than 60/ml/min/1.73m^2. Malignancy was defined as an active malignancy within 20 years. Cognitive frailty was collected and consisted of dementia, cognitive impairment or delirium in admission history[19,24,37].

Statistical analysis

Descriptive statistics (mean with standard deviation and frequencies as percentages) were used to describe sample characteristics.

Model development – Continuous variables were tested for linearity by means of spline curves[38]. Collinearity between covariates was tested and there was no assumption of correlated predictors. Manual backward multivariable logistic regression was applied to select predictors (Akaike information criterion; AIC p<0.157)[15].

Missing data - The extent of missing data was investigated on all predictor variables. If more than 5% of missing values was revealed, multiple imputation was performed by using the multivariate imputation by chained equations procedure [39]. Based on the percentage of missing cases in the variables ASA and mobility (≥50%), we created 50 different imputed datasets. In all prediction models ASA and mobility were not selected after multivariable backward selection and therefore did not include them for further analyses.

Model performance - Quality of the BHFS was assessed with explained variance (Nagelkerke's R^2). Discrimination analysis, the ability to distinguish between outcome groups, was performed using a receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) of 0.70-0.79 was indicated as acceptable, 0.80-.89 as excellent and >0.90 as outstanding discrimination[40]. Calibration, agreement between predicted probabilities of mortality and observed mortality, was assessed in two ways: (i) goodness-of-fit of the model was assessed using Hosmer-Lemeshow (H&L) goodness-of-fit test (p>0.05 point out adequate calibration)[40]; and (ii) calibration plots for both models were provided, ordered observed and predicted probabilities in deciles of the predicted mortality risk.

Several cut-off points and predicted probabilities of 30-day and 1-year mortality for each individual were calculated by using a linear predictor with formula:

$$Probability = \frac{1}{1 + e^{-(lp)}}$$

.

To calculate easy to use risk scores for the BHFS-30 and BHFS-365, regression coefficients of the predictor variables were divided by the lowest regression coefficient, rounded to the nearest integer, and individual scores were summed to determine the total risk score of each patient. Finally sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of the risk score values were calculated, using the same cut-off points to compare classifications of high risk patient groups.

Validation - Internal validation of the BHFS was performed by determining a degree of overfitting in coefficients with bootstrapping and we report optimism-corrected AUC and R^2. Bootstrapping is a method for estimating the sampling distribution of an estimator by resampling with replacement from the original sample[41].

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated before internal validation. All statistical analyses were performed using SPSS version 24.0 (IBM SPSS for Windows, Armonk, NY, USA) and R version 3.4.0 (The R Project for Statistical Computing).

RESULTS

Descriptives

In total 993 patients of 65 years and older were admitted after a hip fracture. Forty-nine of these patients were treated nonoperatively. Nineteen patients were admitted in the inclusion period with a second hip fracture. In total 925 patients were eligible for inclusion.

Baseline characteristics are presented in table 1. The mean age was 81.9 years and 69.8% of the patients were female. Cardiac disease was the most prevalent comorbidity measured at time of surgery (58.1%). Cognitive frailty is seen in 23.1% of the patients. Thirty-day mortality was 9.9% and 1-year mortality was 25%.

Table 1. Baseline characteristics of patients included with a hip fracture

	Total with missing	Total after MI	Total after CCA for development model	30-day mortality group	1-year mortality group
Number of cases (n,%)	925	925	916	91 (9.93)	229 (25.0)
Age (mean years ±SD)	81.9 (7.6)	81.9 (7.6)	81.9 (7.6)	84.8 (6.3)	84.9 (7.3)
Gender (female,%)	647 (69.9)	647 (69.9)	639 (69.8)	59 (64.8)	148 (64.6)
Living in an institution (n,%)	267 (28.9)	267 (28.9)	265 (28.9)	47 (51.6)	113 (49.3)
ASA classification (n,%)					
1-2	133 (30.6)	377 (40.8)	132 (30.5)	4 (8.0)	10 (8.7)
3	247 (56.8)	462 (49.9)	245 (56.7)	26 (52.0)	66 (57.4)
4-5	55 (12.6)	86 (9.3)	55 (6.0)	20 (40.0)	39 (33.9)
Missings	*490*	*0*	*484*	*41*	*114*
Pre-fracture mobility (n,%)					
Freely mobile without aids	202 (47.6)	325 (35.2)	200 (47.5)	12 (25.0)	35 (31.8)
Mobile outdoors with one aid	30 (7.1)	54 (5.9)	30 (7.1)	3 (6.3)	9 (8.2)
Mobile outdoors with 2 aids or frame	148 (34.9)	264 (28.5)	148 (35.2)	24 (50.0)	50 (45.5)
Some indoor, never goes outside	31 (7.3)	166 (17.9)	30 (7.1)	5 (10.4)	11 (10.0)
No functional mobility	13 (3.1)	116 (12.5)	13 (3.1)	4 (8.3)	5 (4.5)
Missings	*501*	*0*	*495*	*43*	*119*
Fracture type (intracapsular, %)	513 (55.5)	513 (55.5)	508 (55.5)	46 (50.5)	116 (50.7)
Hb‡ (mean mmol/L ±SD)	7.97 (1.0)	7.97 (1.0)	7.97 (1.0)	7.43 (1.2)	7.59 (1.1)
Cognitive frailty (n,%)	213 (23.0)	213 (23.0)	212 (23.1)	31 (34.1)	89 (38.9)
Respiratory disease (n,%)	128 (13.8)	128 (13.8)	126 (13.8)	17 (18.7)	40 (17.5)
Cardiac disease (n,%)	536 (57.9)	536 (57.9)	532 (58.1)	56 (61.5)	141 (61.6)
Renal insufficiency† (n,%)	211 (23.0)	211 (23.0)	211 (23.0)	29 (31.1)	72 (31.4)
Cerebrovascular disease (n,%)	148 (16.0)	148 (16.0)	146 (15.9)	19 (20.9)	43 (18.8)
Diabetes (n,%)	165 (17.8)	165 (17.8)	163 (17.8)	20 (22.0)	49 (21.4)
Depression (n,%)	63 (6.8)	63 (6.8)	61 (6.7)	5 (5.5)	17 (7.4)
Malignancy (n,%)	109 (11.8)	109 (11.8)	108 (11.8)	16 (17.6)	37 (16.2)

‡: missings: n=8

†: missings: n=2

Abbreviations: MI: multiple imputation; SD: standard deviation; CCA: complete case analysis; ASA: American Society of Anesthesiologists grade; Hb: hemoglobin

BHFS-30

Backward selection for the BHFS-30 identified the following independent predictor variables: age, gender, living in an institution, Hb, respiratory disease, diabetes and malignancy (table 2). H&L-test was non-significant (p=0.88), and indicated a good fit of this model. Before internal validation the AUC of the model was 0.74 (95% CI 0.68 to 0.79) and Nagelkerke's R^2 was 0.14. After internal validation the AUC of the model was 0.71 (figure 1) and Nagelkerke's R^2 was 0.11. Figure 2 shows the calibration plot of this model.

Table 2. Results of multivariable logistic regression analysis for 30-day mortality (p=0.157)

Factor	Value	Coefficient before internal validation	Coefficient after internal validation	OR‡	95% CI‡
Age	Years	0.042	0.038	1.04	1.01-1.08
Gender	Female	-0.566	-0.510	0.57	0.35-0.93
Living in an institution	Yes	0.928	0.836	2.53	1.58-4.06
Hb	mmol/L	-0.497	-0.448	0.61	0.48-0.77
Respiratory disease	Yes	0.531	0.478	1.70	0.93-3.12
Diabetes	Yes	0.427	0.385	1.53	0.88-2.68
Malignancy	Yes	0.510	0.459	1.67	0.89-3.10
Constant		-2.047	-2.037		

‡: Before internal validation
Abbreviations: OR: Odds ratio; CI: Confidence interval; Hb: hemoglobin

All regression coefficients were transformed into risk scores to facilitate the use of the models for predicting the risk of 30-day mortality. The model for 30-day mortality using these risk scores was:
*1*age - 13*gender + 22*living in an institution - 12*Hb + 13*respiratory disease + 10*diabetes + 12*malignancy.*

The range of the total risk score was -74 to 50. High risk patients (a cutoff of BHFS-30 ≥24) had a predicted 30-day mortality risk of 25% or higher. A total of 52 (5.7%) patients were assigned a high risk. At this cutoff point, sensitivity was 19.7%, specificity was 95.9%, PPV was 34.6% and NPV was 91.6% (table 3). An example of the BHFS-30 for a high risk patient in clinical practice is given in figure 3.

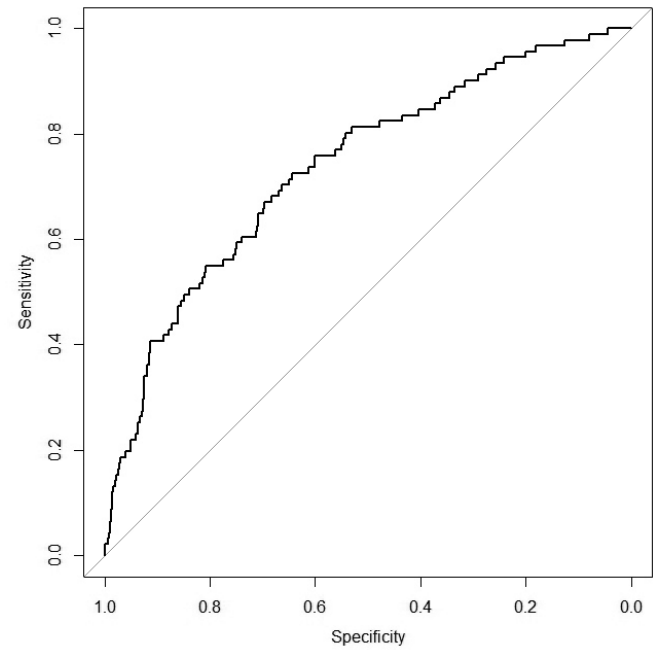

Figure 1. Receiver operating characteristic area under the curve. Discrimination of the Brabant Hip Fracture Score for 30-day mortality

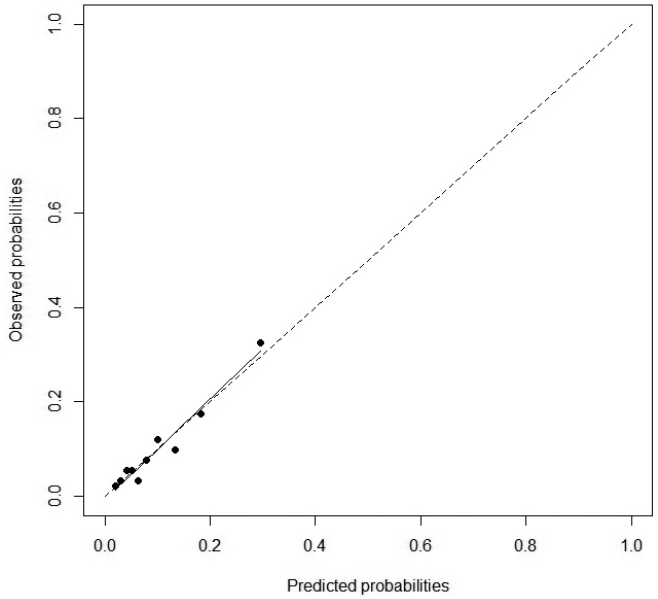

Figure 2. Calibration plot. Observed vs. predicted probabilities of mortality in the Brabant Hip Fracture Score for 30-day mortality

Table 3. Prognostic and predictive values of the BHFS-30 with different cut offs

p_t (%)	BHFS-30	TP	TN	FP	FN	Sensitivity	Specificity	Sensitivity + specificity	PPV	NPV
5	-25	82	240	585	9	90.1	29.1	119.2	12.3	96.4
10	-5	64	545	280	27	70.3	66.1	136.4	18.6	95.3
15	7	47	675	150	44	51.7	81.8	133.5	23.9	93.9
20	15	35	753	72	56	38.5	91.3	129.8	32.7	93.1
25	24	18	791	34	73	19.7	95.9	115.6	34.6	91.6

Abbreviations: p*t*(%): threshold probability of 30-day mortality; BHFS: Brabant Hip Fracture Score; TP: true positives; TN: true negatives; FP: false positives; FN: false negatives; PPV: positive predictive value; NPV: negative predictive value

Patient:

- 82 year
- Male
- Living in a nursing home
- Hb 6.5 g dl^{-1}
- COPD
- Diabetes

Brabant Hip Fracture Score-30

Variable	Value	Points
Age		**1*82**
Gender	Male	**0**
	Female	-13
Living in an institution	Yes	**22**
	No	0
Hb	mmol/L	**-12*6.5**
COPD	Yes	**13**
	No	0
Diabetes	Yes	**10**
	No	0
Malignancy	Yes	12
	No	**0**
Total		**49**

$$Predicted\ 30-day\ mortality\ = \frac{1}{1+e^{-(-2.037+(49\,x\,0.038))}} = 0.46 = 46\%$$

Figure 3. A clinical example of the Brabant Hip Fracture Score for 30-day mortality

BHFS-365

After backward selection the following variables were found to be independent predictors for 1-year mortality: age, gender, living in an institution, cognitive frailty, Hb, respiratory disease, renal insufficiency, diabetes and malignancy (table 4). The H&L-test was 0.42 and reveal a good fit. Before internal validation the AUC was 0.77 (95 CI 0.73 – 0.80) and Nagelkerke's R^2 was 0.23. After internal validation the AUC was 0.75 (figure 4) and Nagelkerke's R^2 was 0.21. The calibration plot of this model is shown in figure 5.

Table 4. Results of multivariable logistic regression analysis for 1-year mortality (p=0.157)

Factor	Value	Coefficient before internal validation	Coefficient after internal validation	OR‡	95% CI‡
Age	Years	0.062	0.058	1.06	1.04-1.09
Gender	Female	-0.727	-0.686	0.48	0.33-0.70
Living in an institution	Yes	0.808	0.762	2.24	1.53-3.29
Hb	mmol/L	-0.410	-0.387	0.66	0.56-0.79
Cognitive frailty	Yes	0.677	0.639	1.97	1.33-2.92
Respiratory disease	Yes	0.646	0.609	1.91	1.20-3.04
Renal insufficiency	Yes	0.299	0.282	1.35	0.93-1.96
Diabetes	Yes	0.473	0.446	1.61	1.06-2.44
Malignancy	Yes	0.597	0.563	1.82	1.12-2.95
Constant		-3.342	-3.2038		

‡: Before internal validation
Abbreviations: OR=Odds ratio; CI: Confidence interval, Hb: hemoglobin

The model for 1-year mortality using the risk scores was:
*1*age - 12*gender + 13*living in an institution - 7*Hb + 11*cognitive frailty + 11*respiratory disease + 5*renal insufficiency + 8*diabetes + 10*malignancy.*

The range of the total risk score was -19 to 77. Table 5 presented several threshold probabilities of the BHFS-365. Using a BHFS-365 ≥53 to predict the probability of 1-year mortality at >50% produced a sensitivity of 23.1%, a specificity 94.5%, a PPV of 58.2% and a NPV of 78.7.

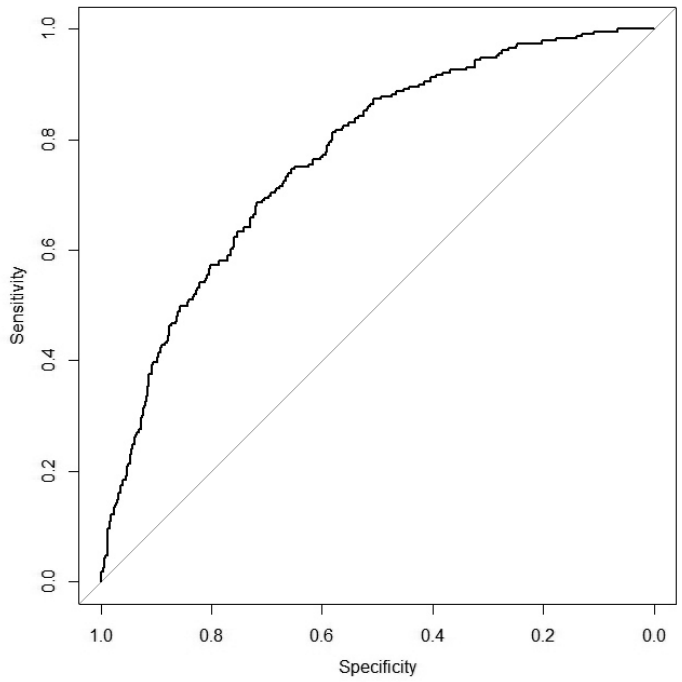

Figure 4. Receiver operating characteristic area under the curve. Discrimination of the Brabant Hip Fracture Score for 1-year mortality

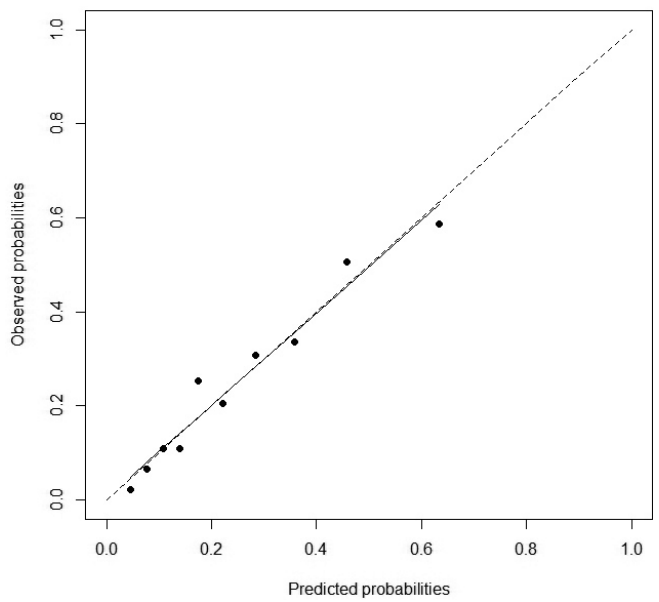

Figure 5. Calibration plot. Observed vs. predicted probabilities of mortality in the Brabant Hip Fracture Score for 1-year mortality

Table 5. Prognostic and predictive values of the BHFS-365 with different cut offs

p_t (%)	BHFS-365	TP	TN	FP	FN	Sensitivity	Specificity	Sensitivity + specificity	PPV	NPV
10	15	220	183	504	9	96.1	26.6	122.7	30.4	95.3
20	29	175	420	267	54	76.4	61.1	137.5	39.6	88.6
30	38	133	535	152	96	58.1	77.9	136	46.7	84.8
40	46	98	610	77	131	42.8	88.8	131.6	56.0	82.3
50	53	53	649	38	176	23.1	94.5	117.6	58.2	78.7

Abbreviations: pt(%) = threshold probability of 1-year mortality; BHFS: Brabant Hip Fracture Score; TP: true positives; TN: true negatives; FP: false positives; FN: false negatives; PPV: positive predictive value; NPV: negative predictive value

DISCUSSION

This study aimed to develop two clinical prediction models (BFHS) for 30-day and 1-year mortality in elderly surgically treated patients after a hip fracture. The BHFS-30 consisted of the following independent predictor variables: age, gender, living in an institution, Hb, respiratory disease, diabetes and malignancy. In addition, cognitive frailty and renal insufficiency, were included in the BHFS-365. Both clinical prediction models are easy to use in clinical practice, showed acceptable discrimination, and adequate calibration after internal validation.

Comparison with literature

Until now, the NHFS and AHFS have shown the best results with respect to discrimination and calibration to predict early mortality following hip fracture surgery[8,11]. In line with these studies age, gender, living in an institution, Hb and malignancy were also included in both BHFS models. Cognitive frailty was included in BHFS-365. Age is also in our data as important predictor of mortality, because aging involves a progressive loss of functional reserve in all organ systems[22]. Our data support the current literature that males have a higher risk of mortality and lose more years of life proportionally[42]. Pre-fracture residence in an institution is a surrogate for overall health in the elderly[25]. Clinicians should be aware that elderly patients with a hip fracture experience a large drop in Hb following surgery which is also a predictor variable for poor outcome in the BHFS[28]. Hu *et al*. provided a systematic review with predictive factors for mortality, including several comorbidities. In the BHFS-30 and BHFS-365, respectively three and five prognostic variables in terms of comorbidities were included as important predictors. Increased risk of mortality by diabetes is

partially explained by modifiable clinical variables such as glycemic control and renal complications[43]. The relationship between the predictor renal insufficiency and mortality in hip fracture patients is complex. Following a hip fracture renal hypoperfusion can occur due to a combination of haemorrhage, hypotension and dehydration and may exacerbated by nephrotoxic medications[44]. One of the hypothesis why malignancy resulted in substantially higher mortality in hip fractures is due to increased metabolic dysfunction following cancer treatment. A hip fracture was supposed to exacerbate this metabolic dysfunction via the inflammatory pathway, thereby resulting in increased mortality[21]. The presence of respiratory disease or cognitive frailty impede the body's ability to maintain homeostasis, especially during the perioperative period. These comorbidities can lead to decreased pulmonary reserve or cognitive dysfunction resulting in perioperative complications and higher mortality[31,45]. So, in contrast with the NHFS and AHFS, we used these explicit medical conditions instead of the semi-quantitative value (≥2) of 'number of co-morbidities'. This semi-quantitative value might not distinguish in an elderly population because in a general population aged 80 years and older 78% have two or more medical conditions at the same time[6]. And besides, in clinical practice the number of comorbidities is often difficult to determine and certain types of comorbidity, included in the BHFS, are known to be significant predictors of 30-day and 1-year mortality[21,25].

In contrast with the AHFS, the BHFS in accordance with the NHFS did not contain ASA and mobility. Included strong predictors among comorbidities in the BHFS, such as respiratory disease, diabetes and malignancy, could be an explanation why mobility and ASA were not selected in the BHFS. Furthermore, ASA is in clinical practice a difficult and subjective method to grade pre-operative health of surgical patients, showed a wide range of inter-rater reliability with moderate to poor agreement and could be unreliable as prognostic variable in prediction models[46,47].

Model performance

After internal validation the AUC of the BHFS-30 was 0.71 and of the BHFS-365 was 0.75. The AUC for 30-day mortality was in line with the development of the NHFS (AUC 0.72). The BHFS-30 and BHFS-365 indicated a good fit corresponding with the NHFS and AHFS of 30-day mortality. A difference with previous studies was the use of AIC, and the use of age and Hb as a continuous, linear term in the BHFS to prevent loss of power[15,48].

For a clinically relevant and meaningful model to guide treatment decisions for elderly patients with a hip fracture, a cutoff might be desirable to classify patients as either low risk or high risk, particularly in predicting early (30 day) mortality. To precisely define the optimal threshold probability for a high risk group is difficult in clinical practice[49]. Informing patients and families about the high risk of mortality following hip fracture and eventually withhold surgery after medical decision making may lead to a difference in outcome. For this reason a high specificity, to avoid false positive cases, is crucial for a risk prediction model in patients with a hip fracture. With a high specificity there is a small number of patients being incorrectly classified and might be unfairly treated nonoperatively. So the cutoff of the BHFS-30 was set at 25%. The NHFS demonstrated one cutoff (>10%) to predict the probability of 30 day mortality, without discussing the level of risk and produced a lower specificity (80.8%). The AHFS assessed a cutoff of 17.9% for defining a high risk group. This cutoff point showed slightly lower specificity than the cutoff of the BHFS-30 ≥24 for high risk. In clinical practice a cutoff of BHFS-30 ≥24 could classify patients as high risk for early mortality and could support clinicians in tailoring treatment for medical decision making in an early phase. Please note that the sensitivity and the PPV are moderate to low, so the BHFS-30 will miss patients who will die within 30 days (n=34; 3.7%) or 1 year (n=38; 4.1%). For 1-year mortality a threshold probability of 50% (BHFS-365 ≥53) could classify patients as high risk. This implies that patients and relatives should be informed about the doubled risk for mortality within 1 year.

Strengths and limitations

A methodological strength of this study is that we internally validated the BHFS by bootstrapping techniques and correctly adjusted for overfitting in contrast with previous hip-fracture prediction model studies[15,41]. Another strength, in contrast with previous studies is that we provide calibration plots to visualize the agreement between the observed and predicted values. Other articles about this topic only report H&L statistic, which provides a P-value for differences between observed and predicted mortality and did not indicate the direction of any miscalibration[9,11]. H&L statistic only is arbitrary and imprecise because P-values hang on the combination sample size and the degree of miscalibration[41]. Miscalibration suggests that clinical prediction models provide biased information and one of our common goals of developing clinical prediction models was to inform clinicians, patients and families in clinical practice for medical decision making, in which calibration is an essential requirement.

Our study has also limitations that merit discussion. The first concern is the small spread in the distribution of the predicted probabilities for the BHFS-30. This model estimate more often a lower risk of mortality compared with a higher risk. For the BHFS all operatively treated patients of 65 years and older in two non-university major 'top-clinical' hospitals were included, and patients with a very high risk of mortality might be treated nonoperatively. However, the effect of exclusion of these patients has most likely limited effect on our risk model for early mortality, because it involved a very small subset of patients. A second limitation, given the available date, is our inability to account for clinical severity of illness among patients with specific medical conditions and this could have influenced the predicted probabilities of mortality. A third limitation was the BHFS did not use the MMSE to score cognitive impairment as suggested by the NHFS, because this test was not available in daily clinical practice. We used a more practical score with cognitive frailty, consisted of dementia, cognitive impairment or a delirium in admission history.

Practical implications

In the Netherlands the Dutch Hip Fracture Audit (DHFA) was introduced in 2016, consistent with the UK National Hip Fracture Database as a multidisciplinary register of quality to monitor and improve quality of hip fracture care[50]. The BHFS may be well embedded in the DHFA for future comparison, both between and within units and longitudinally over time. Future work will assess external longitudinal validation and will evaluate the robustness of the performance of the BHFS in other units.

In conclusion, we demonstrated that the internally validated BHFS for 30-day and 1-year mortality in surgically treated elderly patients with a hip fracture showed acceptable discrimination and adequate calibration. The BHFS consisted of seven and nine combined predictors, respectively, with special attention for comorbidities. In clinical practice a cutoff of BHFS-30 ≥24 could identify frail elderly patients at high risk for early mortality and could support clinicians, patients and families in tailoring treatment for medical decision making.

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CHAPTER 4

Factors influencing the decision-making of treatment for hip fractures in frail patients: A concept mapping study

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ABSTRACT

Introduction: Hip fractures can have devastating impact on survival and functional outcomes among older patients. In the subpopulation of most frail patients with limited life expectancy the decision to undergo operative management (OM) is less straightforward. The objectives were (1) to identify factors that could influence the decision to recommend OM or nonoperative management (NOM) in frail patients with a hip fracture, and (2) to create a decision-support tool to identify patients potentially eligible to discuss NOM.

Material and methods: From January-October 2018 we used a seven-stage concept mapping method: (1) preparation step with developing a focus prompt; (2) brainstorming step to identify factors among hip-fractured patients, relatives and subject matter experts that could influence the decision-making process between OM and NOM; factors were sorted (3) and rated (4) by participants; factors were analyzed by multidimensional scaling and hierarchical cluster analysis (5) and interpreted (6) by a consortium, and (7) operationalized into a decision-support tool by using data from the Brabant Injury Outcome Surveillance. In total, 100 national subject-matter experts were invited to participate in the subsequent data collection activities. We also held semistructured interviews after informed consent with five hip-fractured patients and five relatives to reflect on their decision-making process.

Results: In total, five patients, five relatives and 50 subject-matter experts participated in this study. The decision-support tool consisted of four items: (1) pre-fracture health status; (2) living in an institution; (3) frailty score; and (4) two or more comorbidities. The total score was calculated by summing the scores of the four items. A summing cut-off score of ≥3 represent an optimal cut-off for patients potentially eligible to discuss NOM.

Conclusion: This study generated a decision-support tool of four clinical factors (pre-fracture health status, living in an institution, frailty score, and two or more comorbidities) that could influence the decision for OM or NOM in frail hip-fractured patients. This study expands our understanding of the importance of these factors and provide information to aid providers in shared decision-making for surgical repair or palliative care.

Keywords: Hip fracture, (non) operative treatment, concept mapping, decision-support tool

INTRODUCTION

Hip fracture is a potentially devastating illness for older patients which often results in loss of independence, poorer quality of life (QoL), and a high rate of mortality[1,2]. Hip fractures are typically treated with surgical repair, even if these patients have advanced comorbidities, are institutionalized, or are already bedridden. However, the decision to undergo operative management (OM) versus nonoperative management (NOM) is less straightforward among those frail patients with profound cognitive and functional disability[3]. Hip fractures in these frail patients causes devastating short- and long-term consequences including immobilization, delirium, functional and cognitive decline, and death. In the clinical management of those frail patients with limited life expectancy and poor QoL, a palliative care approach might considered appropriate[4]. Palliative care focuses on improving QoL for patients and relatives by providing an added layer of support, including goals of care discussions, pain and symptom management, care planning and coordination, and end-of-life care[5,6].

Current guidelines have no strict advice for frail patients with a hip fracture, as a result of lack of evidence on palliative care in these patients[7-9]. Moreover, in the NICE guidelines NOM is mentioned briefly, with the assumption that surgery should be done and as fast as possible. However, the 'Choosing wisely campaign' has stimulated shared decision-making for patients at high risk for death or severely impaired functional recovery and suggest patients and their families should offered the alternative of care focused entirely on comfort[10].

In current practice, it is insufficiently transparent which considerations play a role in the shared decision-making for OM or NOM, particularly in frail patients. Various factors that influence the mortality after a hip fracture have been investigated[11-13], but which factors influence the choice of whether or not to operate a frail patient has not been investigated.

The aim of this study was to identify factors that could influence the decision for OM or NOM in frail patients with a hip fracture and develop a decision-support tool to identify patients potentially eligible to discuss NOM.

MATERIAL AND METHODS

Concept mapping

To identify factors that could influence the decision for OM or NOM we used a structured conceptualization methodology known as concept mapping. Concept mapping has been used in a wide variety of studies and is used for building a feasible and valid visual framework based on consensus among the main stakeholders in the field. Concept mapping was introduced by William Trochim in 1989 and can be used by groups to develop a conceptual framework which can guide evaluation or planning[14]. It is a mixed (quantitative/qualitative), participatory, group idea-mapping that integrates group processes such as brainstorming, sorting and rating with a sequence of multivariable statistical methods. A consortium of 7 healthcare providers in the field of management of hip fractures asked subject-matter experts among different types of physicians and surgeons to participate in this study. In total, 100 national subject-matter experts were invited to participate in the subsequent data collection activities. We also held semi-structured interviews after informed consent with five hip-fractured patients and five relatives to reflect on their decision-making process. Ethical approval was received from the Medical Ethics Committee Brabant, the Netherlands (project number NL50258.028.14). This report has been prepared in accordance with SRQR reporting guidelines[15].

The concept mapping procedure comprises seven steps: (1) the preparation step in which the focus prompt for this study was identified and participants were selected; (2) the brainstorming step in which factors involved in the decision-making process between OM and NOM were generated from literature search, and interviews with patients, relatives and the consortium of the Hip fracture decision-support tool; (3) the sorting step in which statements were categorized in different subcategories; (4) the rating step in which statements were rated in terms of feasibility and importance; (5) the analysis step. From the sorting step, a concept map solution was generated by using multidimensional scaling and hierarchical cluster analyses. Mean importance ratings of the clusters were computed by averaging the average rating of each factor in the clusters; (6) the interpretation step. Maps were discussed during consortium meetings and by email. Consensus was obtained regarding the appropriateness of the factors included in the different clusters; and (7) finally the operationalization step in which was developed a decision-support tool. Table 1 summarizes the concept mapping procedure used in this study supported by using Concept Mapping software (Concept Systems; www.conceptsystems.com).

Table 1. Overview of the Concept Mapping procedure used in this study

Step	Explanation
1. Preparation	
Consortium:	Developing the focus prompt
Participants:	
- Hip-fractured patients and relatives	Hip fractured patients and relatives were asked to reflect on their decision-making process
- Subject-matter experts	- physicians: general practitioners, elderly care physicians, anesthesiologists, geriatric medicine specialists - surgeons: trauma and orthopaedic surgeons - clinical ethicist
2. Brainstorming	
A combination of data collection methods:	Objective: To identify factors that could influence the decision to recommend OM or NOM in frail patients with a hip fracture
- Literature search	- Keywords: hip fracture, OM, NOM, patient-specific factors (e.g. elderly, frailty, comorbidity), outcome (e.g. mobility, QoL, mortality) - Search performed in January 2018 in PubMed
- Semistructured interviews	5 interviews with patients 5 interviews with relatives 6 interviews with consortium of the Hip fracture decision-support tool
- Document analysis	The consortium distilled a list of potential factors, which were involved in the decision-making process between OM, NOM. Factors were edited for clarity, and duplicate factors were eliminated.
3. Sorting of factors	*Concept Systems*
- Sorting by participants	Participants organized the entire database of factors into groups or themes based on similarity of the factors. Each factor was placed in only one cluster, but participants used as many clusters as they wish.
4. Rating of factors	*Concept Systems*
- Rating by participants	Participants rated the full list of factors using a predefined 6-point scale of how important they thought each factor would be for them if they had to choose between OM and NOM (1 means ‘not important at all’ and 6 means ‘very important’).

Table 1. Continued.

Step	Explanation
5. Analysis	*Concept Systems*
- Multidimensional scaling	Step 3 results in a point map. The proximity of the points represents the frequency in which the factors were sorted into the same cluster by the experts and factors that are closer together indicate higher degrees of similarity based on sorting.
- Hierarchical cluster analysis	The factors on the map were grouped into non-overlapping clusters. Factors that show a high level of coherence end up in one cluster.
6. Interpretation	
- Consortium	- A range of cluster solutions was examined in a reverse stepwise cluster-reduction process[16]. In this process, two clusters merge (e.g., from 7 to 6 clusters) at each reverse step. - At each level the members of the consortium judged the conceptual and interpretive sense until the fewest number of clusters were reached but still retained the maximum amount of information. - Labels of the clusters were suggested by the consortium.
7. Operationalization	
- Consortium	Developing a decision-support tool

OM, operative management; NOM, nonoperative management; QoL, Quality of Life;

Decision-support tool

To identify the patient population that might be eligible to discuss NOM, a decision-support tool was developed using data derived from concept mapping. The decision-support tool is a clinician-administered instrument to facilitate the identification of patients with a hip fracture eligible to discuss NOM. To assess whether the decision-support tool was able to capture clinical differences, we examined 1-year mortality for patients with a summing score above and below the cut-off score on the decision-support tool. For this purpose, we used data from the Brabant Injury Outcome Surveillance (BIOS). BIOS is a multicenter prospective observational cohort study with a follow-up of twelve months after hip fracture[16]. This study provide data on survival, pre-injury status, comorbidities, frailty, health status (HS), and QoL about 821 surgically treated older patients with a hip fracture.

RESULTS

Patient and expert participation

In total, five patients and five relatives participated in interviews in the brainstorming step about important factors considering OM and NOM. A total of 50 subject-matter experts (50% of total eligible participants) participated in sorting and rating of the factors. These experts had on average 12.0 years of experience and 18% were female (Table 2). Subject-matter experts were represented from all kind of physicians (general practitioners, elderly care physicians, geriatric medicine specialists, surgeons, anesthesiologists) and residents involved in daily hip fracture care in the Netherlands.

Table 2. Baseline characteristics of participants of the sorting and rating of the factors with Concept Systems software.

Characteristic	n=50
Age (years)	42.3 (SD 10.0)
Sex (female, %)	18.0%
Years of experience	12.0 (SD 8.2)
Subject matter experts (n, %)	
- general practitioners/elderly care physicians	14 (28.0)
- geriatric medicine specialists	6 (12.0)
- surgeons	10 (20.0)
- anesthesiologists	6 (12.0)
- residents	11 (22.0)
- other (clinical ethicist)	3 (6.0)

Concept mapping

The brainstorming step resulted in a list of 52 mutually exclusive factors, which could influence the decision-making process between OM and NOM in frail patients with a hip fracture (Appendix A). The subject-matter experts sorted the factors into an average of 6.42 clusters (SD 1.69). After analysis by using Concept Systems software, in the interpretation phase the consortium reduced the number of clusters step by step. We analyzed each step, taking into account the clusters being grouped together in that step and the content represented by the newly formed clusters. First, in examining the interpretability of the initial 8 cluster solution, the consortium noticed that in the step from 5 to 4 clusters, 2 clusters merged that seem to have a different content. Finally a 5-cluster map was selected and labels were developed for each cluster. Figure 1 shows the

final concept map with the following five clusters: (1) QoL and needs/wishes of the patient, (2) pre-fracture function, (3) surgical risk prediction, (4) comorbidity, and (5) logistical factors.

Table 3 shows ranking of the clusters by the mean for importance, ranged between 2.24 and 4.02. Cluster 1 (Qol and needs/wishes of the patient; M=4.02) had the highest mean importance rating followed by cluster 2 (pre-fracture function; M=3.87) and cluster 3 (surgical risk prediction; M=3.79). No consistent significant differences were found between mean importance ratings of the clusters.

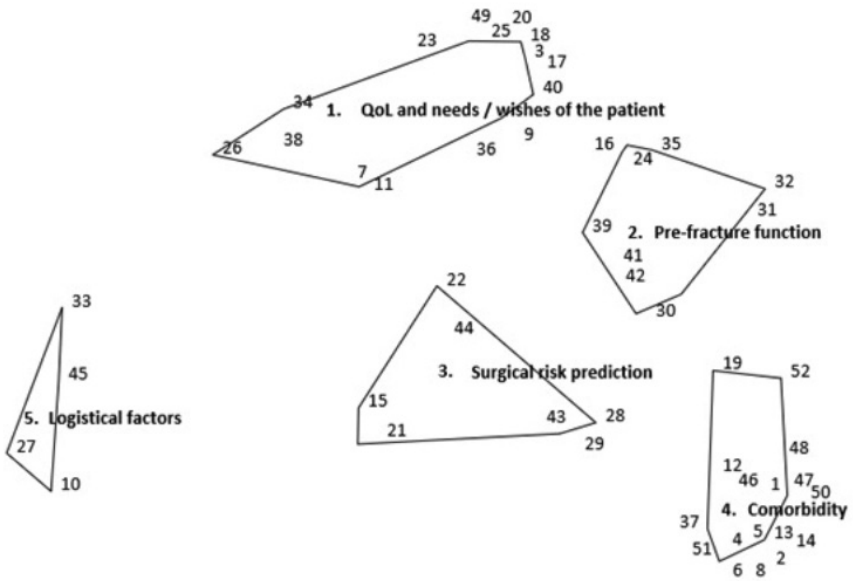

Figure 1. Concept map of the main factors for decision-making between operative management and nonoperative management in frail patients with a hip fracture. Clusters represent the overarching conceptual domains of the 52 factors. Numbers correspond to the factors that were sorted into each cluster.

Table 3. Ranking of the clusters and the corresponding factors from the concept mapping

Concept Mapping Clusters	Factors[a]	Importance	
		Mean rating[b]	Ranking
QoL and needs/wishes of the patient	Needs and wishes of the patient Expected quality of life after hip fracture surgery Advance directive of no treatment	4.02	1.
Prefracture function	Prefracture bedridden patient Prefracture ADL function Prefracture living in an institution	3.87	2.
Surgical risk prediction	The degree of surgical risk Life expectancy at time of hip fracture The degree of risk for postoperative complications	3.79	3.
Comorbidity	Pulmonary reserve Cardiac function Cognitive frailty	3.64	4.
Logistical factors	Time for clinician to evaluate NOM with patient, relatives and other health-care professionals Shortage of facilities, including staff occupation and operating rooms	2.24	5.

[a] Factors for which there was the most consensus among participants regarding the categorization within the cluster.
[b] Mean importance ratings of the clusters were computed by averaging the rating of each factor in the clusters.
QoL, Quality of Life; ADL, Activities of Daily Living; NOM, nonoperative management

Decision-support tool

The clusters were transformed by consensus from the consortium into the decision-support tool as follows (Table 4): Cluster 1 (QoL) Patient's pre-fracture HS; Cluster 2 (Pre-fracture functioning) Whether the patient was living at home or in institution; Cluster 3 (Surgical risk prediction) Patient's pre-fracture frailty score; Cluster 4 (Comorbidity) Whether a patient had 2 or more comorbidities[17]. Cluster 5, logistical factors, represented the conditions for performing surgery. If there are no facilities available, OM is not a treatment alternative, and the decision tool cannot be used (as the outcome will always be NOM). Therefore, this cluster was not included in the overall decision-support tool.

Each cluster was operationalized as a dichotomous item (yes/no). The total score is calculated by summing the scores of the four items and ranges from 0 to 4. A summing cut-off score of ≥3 represent a clinically optimal cut-off point for

patients potentially eligible to discuss NOM. A complete version of the hip fracture decision-support tool is presented in appendix B.

The decision-support tool could be retrospectively completed for 528 patients using the BIOS dataset. HS was operationalized as an EQ-5D Visual Analogue Scale (VAS)[18] value below 50. Frailty was operationalized as a score of 4 or higher on the Groningen Frailty Index (GFI)[19]. The mean sum score on the decision-support tool was 1.47. The majority of patients (55%) had a summing score of 0 or 1. A total of 86 (16.3%) and 44 (8.3%) patients had a summing score of 3 or 4, respectively. These patients would be identified as being eligible for discussing whether NOM would be a treatment option. Figure 2 shows the survival curves of patients with a summing cut-off score of <3 and with a summing cut-off score of ≥3, respectively a one-year survival rate of 90.2% (95% CI 86.5-93.0), and 64.1% (95% CI 54.3-72.3).

Table 4. Items, response options and scoring system of the hip fracture decision-support tool

Item		Response options	Score
1.	Prefracture health status:	Yes	1
	Indication: EQ-5D VAS <50	No	0
2.	Living in an institution	Yes	1
		No	0
3.	Frailty score:	Yes	1
	Indication: GFI ≥4	No	0
4.	2 or more comorbidities	Yes	1
		No	0

EQ-5D VAS, EuroQol-5 dimensions visual analogue scale; GFI, Groningen Frailty Indicator

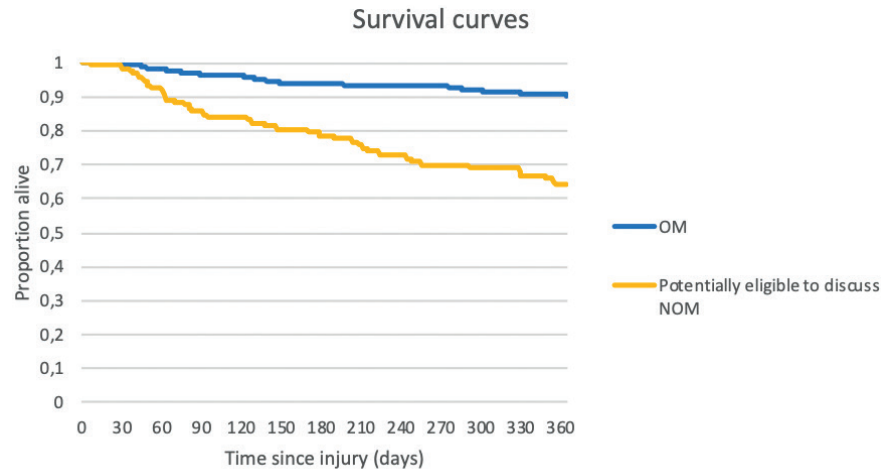

Figure 2. Survival in days for patients with a summing score <3 (OM) and ≥3 (potentially eligible to discuss NOM) on the decision-support tool.
OM, operative management; NOM, nonoperative management

DISCUSSION

Drawing on interviews with patients and relatives, clinical expertise and literature search, we conducted a concept mapping procedure to identify factors that could influence the decision for OM or NOM in frail patients with a hip fracture. Although, NOM has largely been abandoned, as the benefits of prompt surgical care have become clear, the role of NOM could be underestimated in the frailest group of patients that can be nursed with comfort and dignity in the last days and weeks of life[3,4]. In those patients at high risk for death or severely impaired functional recovery, early integration of palliative care is considered appropriate with particular focus on goals of care discussions and end-of-life care[5,6].

This study resulted in a set of 52 factors deemed potentially relevant for medical decision-making in frail patients with a hip fracture. After analyzing, using sorting and rating assignments, our final concept map included five meaningful clusters: (1) QoL and needs/wishes of the patient; (2) pre-fracture function; (3) surgical risk prediction; (4) comorbidity; and (5) logistical factors. To our knowledge, this is the first time that factors that could influence the decision-making process between OM and NOM in frail hip-fractured patients are appraised, refined and complemented by clinical expertise. This work explored the opinions of patients, relatives and subject-matter experts regarding early palliative care interventions

in patients with fragility hip fractures, to aid the design of the most appropriate interventions.

At cluster level, a cluster with relatively low mean importance rating appear to cover logistical factors. Clusters with higher importance ratings were QoL and pre-fracture function. Among QoL, needs and wishes of the patient and advance directive of no treatment are quite understandable. However, in current practice an advance directive of no treatment is rarely seen and individuals fail to complete an advance directive[20]. They seldom discuss their medical treatment preferences, often leaving clinicians with little indication for how they want to be treated[21-23]. Berry et al. described in hip-fractured nursing home residents with advanced dementia that directives to avoid future hospitalizations were also rare[3]. However, goals of care discussion is essential in this frail population and needs to incorporate prognostic information about the overall poor rates of survival and functional recovery. Discussions should anyway take place at the onset of hip fracture, or earlier in older patients at high risk for falls and traumatic fracture, known as advance care planning[24]. Advance care planning is a process whereby a patient, in consultation with healthcare providers and relatives makes decisions about his/her future healthcare, and has been shown to improve patient outcomes and satisfaction, and reduced the incidence of anxiety, depression and post-traumatic stress in surviving relatives[25].

The clusters were operationalized in a decision-support tool. Pre-fracture functioning was operationalized with living in an institution. Outcomes after hip fracture are worse among nursing home residents than among community-dwellers[26-28]. Among hip-fractured nursing home residents not totally dependent at baseline, Neuman and colleagues noted 53.5% died or developed new total dependence within 180 days[1]. Among those individuals who had some degree of functional independence at baseline, one out of two had either died or developed new total dependence within 180 days after fracture. Prior research among healthcare proxies involved in the care of nursing home residents with advanced dementia indicates that the majority of these proxies prioritize comfort-focused care, and only a minority opt for life-prolonging care[29]. Other high importance ratings were given to the degree of surgical risk and complications, and life expectancy at time of hip fracture. These factors are less objective and could be hard to assess in clinical practice.

Surgical risk was operationalized into frailty, a clinical state of increased vulnerability[30], and is associated with adverse outcomes in older post-surgery patients, including prolonged length of stay, complications and postoperative mortality[31].

Logistical factors were not included in the decision-support tool, because these factors are a crucial precondition to apply the decision tool (i.e. the availability of time for clinician to evaluate NOM and surgery room availability). Furthermore, the dataset only contained patients who had received OM; implying that for all of these patients the facilities were available, leading to the same value for all patients if logistical factors had been included in the decision tool.

Two remarkable factors play a minor part in the decision-making process between OM and NOM: age and gender. In literature these predictor variables affect the risk on mortality[32,33], nonetheless clinical subject matter experts involved in this study rated these two predictor variables as far less important. An explanation could be that risk factors, such as frailty status and living in an institution prior to fracture actually determined the risk on mortality, but were not included in those risk models.

Strengths and limitations

A strength of this study is the use of concept mapping. This method enabled collaborative knowledge modeling with subject-matter experts. It also facilitates the creation of shared vision and shared understanding within the field of hip fracture treatment. Randomized trials comparing NOM with OM are difficult in contemporary practice because of ethical issues. Clinicians would be faced with performing surgery on patients with a high risk of dying perioperatively or with withholding surgery from patients who are very likely to benefit from an operation. The factors found to be important in the current study are likely to be useful to inform treatment decisions in frail patients with a hip fracture in other hospitals in the Netherlands and in other geographical areas as well. However, a challenge associated with the concept mapping method is the interpretation of results. It highlights the similarities between and clustering of items, but a limitation of the approach is the inability to describe or explore the relationships between clusters. We operationalized the concept mapping clusters into a decision-support tool. These variables were chosen from available data from BIOS, which was associated with limited clinical validation of choices. The use of summating the number of co-morbidities as semi-quantitative value might

appear controversial to some. However, this number of two or more should not be regarded as any more or less rigorous in considering whether a patient has a relatively good or worse health outcome[34]. We are aware of the problems with assessing pre-fracture HS and frailty. This can introduce recall bias and often self-reported proxies were used as markers to canvass the domains. However, in clinical practice HS could be easily measured with self or proxy-rated HS (e.g. EQ-5D VAS). Frailty instruments, such as GFI, need to be time-efficient and suitable for application in clinical practice in acute surgical patients. Clinical experts indicated that approximately 5% of the patients would be eligible for NOM. The BIOS study showed that 24.6% of patients would be identified by the decision-support tool as potentially eligible to discuss NOM. Particularly in those patients at the end-of-life stage shared decision-making should incorporate patient values and perspectives to help both patient, relatives and healthcare providers to the optimal treatment choice, whether OM or NOM.

Practical implications

Hip fracture in frail patients is challenging and an important opportunity to reassess patients' personal healthcare priorities[35]. On an acute trauma ward, palliative care discussions may not be prioritized, and junior medical staff may lack the confidence and education to conduct these discussions. The decision-support tool developed using concept mapping aimed to identify those patients potentially eligible to discuss NOM. The decision-support tool provides information for the discussion to aid providers in shared decision-making for surgical repair in frail patients. In particular, patients with a cut-off score ≥3, i.e. patients with a relatively poor prognosis, might be eligible to discuss NOM. Patients with a good prognosis will not be treated differently when the decision-support tool will be used; i.e. they would receive OM either way. The decision-support tool was tested in the BIOS and discriminates well for survival. However, future testing of the decision-support tool is required before it can be used in the decision-making process in the treatment of hip fractures. Future studies should evaluate the quality of prediction of our decision-support tool. Additionally research is needed to evaluate patients' QoL and satisfaction with the outcome for relatives and healthcare professionals. The decision-support tool should be validated by being applied prospectively to another cohort of patients, to determine how it would affect their care and what the implications are on the quality of dying and death after decision-making. Also testing for external validity of our decision-support tool is a necessity in order to judge its applicability in general. Future studies should test its suitability in similar groups of patients but in different healthcare

systems to extend its cross-national robustness. Preconditions should be a high standard of palliative care and the ability from healthcare providers and relatives that both treatment options are open to discussion. This could be challenging in the implementation of the decision-support tool.

The results of this study support and enhance personalized medicine, in which patient management is tailored to the individual patient needs. Future perspective will show that there is an opportunity to improve quality of care regardless of how hip fractures in frail patients are managed.

Conclusions

In conclusion, this study revealed a decision-support tool of four factors that influence the decision-making process for OM or NOM in frail patients with a hip fracture: pre-fracture HS, living in an institution, frailty score, and two or more comorbidities. This study expands our understanding of the importance of these factors and provides information to aid providers in shared decision-making for surgical repair or palliative care within frail patients.

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SUPPLEMENTAL FILES

Appendix A. List of factors in the decision-making process in hip fractures

Factor	Factor number	Mean rating
Pulmonary reserve	1	4,2381
Diabetes mellitus	2	2,3333
Ability to do any of the things that make the patient feel valued	3	3,5714
Severity of aortic valve stenosis	4	4,2381
Heart failure	5	4,1667
Use of anticoagulants	6	2,4286
Possibility of successful pain reduction for the patient with NOM	7	4,6190
Pulmonary hypertension	8	3,7857
Expected self-reliance after treatment	9	4,1190
Shortage of facilities, including staff occupation and operating rooms	10	1,8095
Possibility of successful comfort for the patient with NOM	11	4,6190
Patients who sustained an initial hip fracture	12	2,0238
COPD GOLD stage 4	13	4,4048
Severity of peripheral artery disease	14	3,3095
Type of hip fracture: intracapsular vs. extracapsular	15	2,5000
Pre-fracture living in an institution	16	3,6429
Patients' level of thinking about the future with concern	17	2,9524
Satisfaction of the patient to perform everyday activities	18	3,7619
Risk of delirium	19	3,1429
Patients' satisfaction with degree support from others	20	2,9048
Type of hip fracture: displaced vs. undisplaced fracture	21	2,9762
Level of pain following hip fracture	22	3,7143
Satisfaction with living conditions	23	3,9048
Pre-fracture Activities of daily living (ADL) function	24	4,2857
Patients' satisfaction with degree of love and friendship from others	25	2,6905
Needs and wishes of relatives	26	3,5476
Time for clinician to evaluate NOM with patient, relative and other health care professionals	27	1,9286
The degree of risk for postoperative complications	28	4,5000
The degree for surgical risk	29	4,7143
Patient gender	30	1,4286
Degree of pre-fracture mobility	31	4,3333
Pre-fracture bedridden patient	32	4,9048
Treatment preferences of physicians	33	2,6190
Needs and wishes of the patient	34	5,4048
Ability to be independent	35	4,1667
Expected quality of life after hip fracture surgery	36	5,1667

Appendix A. Continued

Factor	Factor number	Mean rating
The degree of left ventricular ejection fraction	37	3,8571
Advance directive of no treatment	38	5,1190
Patients' possibility to postoperatively undergo the rehabilitation trajectory	39	4,1905
Satisfaction of patient with pre-fracture health status	40	3,7143
Postoperative life expectancy	41	4,5476
Life expectancy at time of hip fracture	42	4,5714
Patient age	43	2,6667
Probability of succes of surgery	44	4,3095
Physician's perspective on recovery after hip fractrure	45	2,5952
American Society of Anesthesiologists (ASA) Classification	46	3,6905
An active malignancy	47	4,0952
Cerebrovascular accident with residual deficit	48	3,7857
Possibility to have enjoyment and pleasure in life	49	4,1429
Parkinson disease	50	3,6190
Pneumonia at onset of hip fracture	51	4,4524
Degree of cognitive frailty (history of dementia or delirum)	52	4,3810

Appendix B. Hip fracture decision-support tool: operative versus nonoperative management

Erasmus School of Health Policy & Management

Hip fracture decision-support tool: operative versus nonoperative management
Version 1.0

Objective

The decision-support tool was developed to aid clinicians in the identification of subgroup of patients with a hip fracture eligible for nonoperative management. This decision-support tool is a 4-item clinician-administered instrument. It is designed for use in the emergency department for elderly patients with a hip fracture. The total score is calculated by summing the scores of the four items and ranges from 0 to 4.

The instrument is a tool for the assessment of frail patients with a hip fracture potentially eligible to discuss nonoperative treatment. It is possible to deviate from the outcome of the list, taking patients' and relatives' preferences into account.

Completing the decision-support tool will take up to 5 minutes.

Your findings are relevant for shared decision-making with patient and relatives, and for multidisciplinary consultation (surgeon, anesthesiologist, geriatrician)

ZonMw

This work was funded by the Netherlands Organization for Health Research and Development

Hip fracture decision-support tool Version 1.0

Name of patient:

Patient medical record number:

		Response options	Score
1.	Has the patient a poor prefracture health status? Indication: EQ Visual Analogue Scale <50	Yes No	1 0
2.	Does the patient live in an institution?	Yes No	1 0
3.	Is the patient frail? Indication: Groningen Frailty Indicator ≥4	Yes No	1 0
4.	Does the patient have 2 or more comorbidities?	Yes No	1 0

Total summing score of ≥3?

Yes -- > This patient with a hip fracture is potentially eligible to discuss nonoperative treatment

No -- > For this patient is surgery the preferred treatment

PART II

Quality of Life and psychological distress

CHAPTER 5

Effect of frailty on Quality of Life in elderly patients after hip fracture: a longitudinal study

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ABSTRACT

Introduction: The aims of this study were to examine the pattern of changes over time in health status (HS) and Quality of Life (QoL) in the first year after hip fracture and to quantify the association between frailty at the onset of hip fracture and the change in HS and QoL 1 year later. The major hypothesis was that frailty, a clinical state of increased vulnerability, is a good predictor of QoL in patients recovering from hip fracture.

Material and methods: In this multicenter prospective observational follow-up cohort study we included patients aged 65 years and older, or proxy respondents for patients with cognitive impairment. The primary outcomes were HS (EuroQol-5 Dimensions questionnaire; EQ-5D) and capability wellbeing (ICEpop CAPability measure for Older People; ICECAP-O). Prefracture frailty was defined with the Groningen Frailty Indicator (GFI), with GFI ≥4 indicating frailty. Participants were followed up at 1 month, 3 months, 6 months and 1 year after hospital admission.

Results: Of 1091 eligible patients, 696 (64%) responded to the questionnaires. In total, 371 patients (53.3%) were considered frail. Frailty was negatively associated with HS (β -0.333; 95% CI -0.366 to -0.299), self-rated health (β -21.9; 95% CI -24.2 to -19.6), and capability wellbeing (β -0.296; 95% CI -0.322 to -0.270) in elderly patients 1 year after hip fracture. After adjusting for confounders, including death, prefracture HS, age, prefracture residential status, prefracture mobility, ASA and dementia, associations were weakened but remained significant.

Conclusion: We revealed that frailty is negatively associated with QoL 1 year after hip fracture, even after adjusting for confounders. This finding suggests that early identification of prefracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

Keywords: hip fracture, frailty, Quality of Life, elderly

INTRODUCTION

A hip fracture is a serious event in the elderly population. It is associated with high mortality, morbidity and disability for those who survive[1-3]. Hip fracture risks rise exponentially with increasing age. With the rising longevity across the globe, it seems reasonable that hip fractures will remain an important global health problem with substantial socioeconomic costs[4,5]. A hip fracture has a major impact on health status (HS) and Quality of Life (QoL)[6]. HS represents the perceived impact of a disease on the level of patients' physical, emotional and social functioning[7]. Several factors are negatively associated with HS in elderly patients with a hip fracture, including female gender, comorbidity, poor nutritional status, severe post-surgical pain perception, long duration of hospital stay, postoperative complications, and low physical or psychosocial functioning at prefracture, including cognitive dysfunction[6]. QoL is a multidimensional concept including both positive and negative aspects of life, and it measures patients' evaluation of functioning in line with their expectations[8]. QoL in older people is limited by an individuals' loss of ability to pursue different attributes with regard to attachment, role, enjoyment, security and control[9]. This multidimensional concept can be measured with a capability wellbeing instrument in frail older adults following a hip fracture[10,11].

Inconclusive evidence was found for the predictive value of older age[6]. However, aging is associated with a decline in physiological reserves, which impedes the body's ability to withstand and recover from major and minor challenges, e.g., a hip fracture. This phenomenon is defined as frailty, a clinical state of increased vulnerability, and it interacts with psychological factors, such as emotional state, coping style and sociological state[12].

A systematic review from Lin and colleagues demonstrated that frailty is associated with adverse outcomes in older post-surgery patients, including prolonged length of stay, complications and postoperative mortality[13]. However, the relationship between frailty and HS, and between frailty and capability wellbeing, is unknown. The aims of this study were to (i) compare HS by frailty status at the time of hip fracture, (ii) describe the patterns of HS and capability wellbeing in the first year after hip fracture, and (iii) quantify the association between frailty at the onset of hip fracture and the patterns in HS and capability wellbeing 1 year following a hip fracture. We hypothesized that frail hip-fractured patients would experience

a higher likelihood of poor HS and capability wellbeing, even after accounting for traditionally measured clinical risk factors.

MATERIAL AND METHODS

Study design and participants

The Brabant Injury Outcome Surveillance (BIOS), a multicenter prospective observational follow-up cohort study, was conducted to obtain data at 1 week and 1, 3, 6 and 12 months after hip fracture. Full details of the study, objectives and methods are described in detail elsewhere[14]. Ethical approval was received from the Medical Ethics Committee Brabant, the Netherlands (project number NL50258.028.14). This report has been prepared in accordance with the STROBE guidelines[15].

All participants were included between August 2015 and November 2016 from the ten participating Dutch hospitals and were invited during hospital admission or within several days post-trauma by mail. Both patients aged 65 years and older and proxy respondents for patients with cognitive impairment were eligible for inclusion. Proxy participants could participate from 1 month onwards. Exclusion criteria were as follows: (i) pathological hip fractures, (ii) patients and proxy respondents being unable or unwilling to give written informed consent, and (iii) patients with insufficient knowledge of the Dutch language.

Data collection

Baseline prefracture information (T0) was gathered 1 week or 1 month after hip fracture by self- or proxy-reported questionnaires. The following data were collected at baseline within 1 month after hip fracture: demographic characteristics (age, gender, educational level), American Society of Anesthesiologists (ASA) grading, mobility, degree of frailty and HS. All participants were followed-up at 1 week (T1), 1 month (T2), 3 months (T3), 6 months (T4) and 1 year (T5) after hospital admission. At follow-up sessions, questionnaires were sent to the participant or proxy. In cases of no return, they were contacted by telephone several times. If this method failed, the participant or proxy was considered to be a non-responder at that follow-up time point.

Patient and public involvement

Patients were involved in the recruitment to and conduct of the study. In a small pilot before inclusion in the BIOS, patients were asked their findings about

the questionnaire and outcomes. We made small adjustments and results were disseminated to study participants who want to receive information by a newsletter.

Outcome assessment questionnaires

The Groningen Frailty Indicator (GFI) questionnaire was used to identify elderly individuals as being frail. The GFI is a 15-item self-reported instrument and screens for the loss of function and resources in four domains of functioning: physical, cognitive, social and psychological (supplemental file)[16]. The sum score of the GFI ranges from 0 to 15, with a score of ≥4 indicating frailty. The study of Peters et al. concluded that the GFI is a feasible, reliable and valid self-assessment in home-dwelling and institutionalized elderly people by detecting those at high risk for poor outcomes[17].

The score on the EuroQol-5 Dimensions (EQ-5D), a measure of HS[18]. The EQ-5D has two parts: a visual analogue scale (VAS), which measures self-rated health, and an instrument along five health domains related to daily activities, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. A respondent's EQ-VAS presents self-rated health on a vertical scale with two endpoints, i.e., 'best imaginable health state' (100) and 'worst imaginable health state' (0). Each dimension consists of a three-level response: no problems, moderate problems or severe problems. A scoring algorithm is available by which each health status description can be expressed into an overall score using a published utility algorithm for the Dutch population. HS was assessed with the utility score (EQ-5D™ utility), ranging from 0 representing death to 1 for full health. A negative utility score indicates a health status worse than death. The Dutch tariffs were used for this study to calculate EQ-5D-3L™ preference weights[19]. The EQ-5D has good measurement properties and could be used to measure outcomes for patients recovering from hip fracture[11].

The ICEpop CAPability measure for Older People (ICECAP-O) provides a broad assessment of capability wellbeing as it measures an individual's ability to 'do' and 'be' the things that are important in life[20]. This index of capability focuses on wellbeing defined in a broader sense, rather than defined by health, and covers the following five attributes: attachment (love and friendship), security (thinking about the future without concern), role (doing things that make you feel valued), enjoyment (enjoyment and pleasure), and control (independence). These attributes are used to calculate a tariff between 0, meaning no capability,

and 1, representing full capability. The ICECAP-O has been validated in different elderly populations and for this study the population of Makai et al. of post-hospitalized older people in the Netherlands was used to compare scores[21,22]. The questionnaire shows good convergent validity with health and wellbeing instruments and is able to discriminate between elderly individuals with various health profiles[21,23,24].

Statistical analysis

The descriptive statistics of the cohort were presented as the means with standard deviations (SDs) for continuous variables and as numbers and percentages for dichotomous or categorical variables. Missing baseline characteristics and missing sum scores in EQ-5D and ICECAP-O were imputed according to multiple imputation, using the multivariate imputation by chained equations (MICE) procedure[25]. There were no variables with 5% or more missing values. The dataset was imputed 15 times with 5 iterations. Patient demographics (age, gender) were compared between responders and non-responders. Univariate and multivariable linear regression models were used to compare HS by frailty status at time of hip fracture. To assess the association between frailty and QoL over 1 year, we used linear mixed model analyses for EQ-5D utility scores and ICECAP-O scores, and we used binary logistic mixed model analyses for domains of the EQ-5D. Multicollinearity was assessed with the variance inflation factor (VIF). After univariate analyses, we performed adjusted analyses in which confounders (prefracture HS, sociodemographic variables and comorbidity) were included in the model. Because the mortality of study participants caused drop-out (loss to follow-up), we performed death-adjusted analyses to adjust for overly optimistic estimates of patient outcomes. According to Parsons et al., we assumed that the EQ-5D score ranges from zero to death; these observations were then carried forward to subsequent assessment occasions[26]. Effects were expressed as regression coefficients (Beta; β), odds ratios (ORs), and adjusted ORs (aORs) with 95% confidence intervals (CI), representing the longitudinal association between frailty and HS and between frailty and capability wellbeing over time, reflecting both the within- and between-subject relationship[27]. Statistical test results were considered significant at a level of $p<0.05$. The statistical analyses were performed in SPSS version 24.0 (IBM Statistical Package for Social Sciences, Armonk, NY, USA) and R version 3.4.0 (The R Project for Statistical Computing).

RESULTS

Study population

Figure 1 shows the flow diagram of study participants. Only patients who completed the prefracture questionnaire, including the GFI, were included in this study. No significant differences were found in patient demographics (age: p=0.215; sex: p=0.183) between responders and non-responders. In total, 696 patients were included, and 371 patients (53.3%) were considered frail. Table 1 shows patients' characteristics and clinical parameters, divided into frail and non-frail participants. In total, the mean age was 80.3 years, and 70.4% of the sample was female. Furthermore, 216 (31.0%) proxy participants were included.

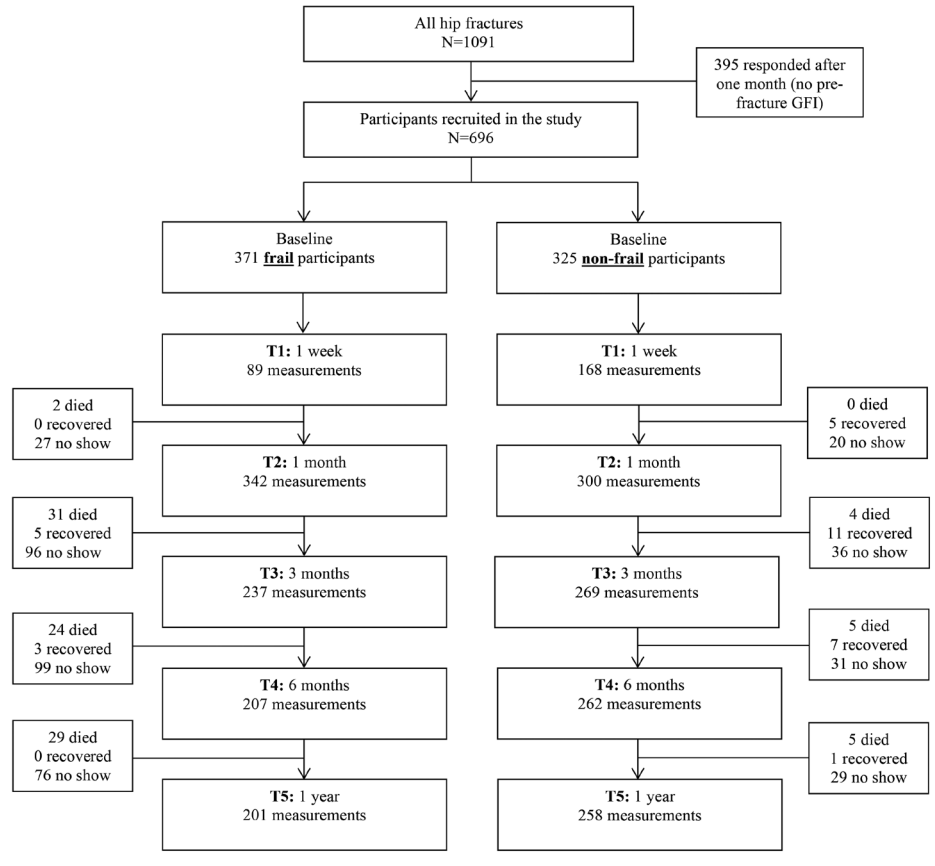

Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'. GFI, Groningen Frailty Indicator; T1, 1 week; T2, 1 month; T3, 3 months; T4, 6 months; T5, 1 year.

Table 1. Demographic and clinical baseline characteristics of the cohort.

Variables	Total	Frail	Non-frail
N	696	371 (53.3)	325 (46.7)
Female (N,%)	490 (70.4)	279 (75.2)	211 (64.9)
Age (mean, SD)	80.27 (8.62)	83.7 (7.67)	76.4 (7.94)
BMI (mean, SD)	24.7 (4.92)	24.3 (4.61)	25.2 (5.19)
Educational level[a] (N,%)			
Low	495 (71.1)	284 (76.5)	211 (64.9)
Middle	107 (15.4)	57 (15.4)	50 (15.4)
High	94 (13.5)	30 (8.1)	64 (19.7)
Prefracture living in institution (N,%)	151 (21.7)	140 (37.7)	11 (3.4)
Prefracture mobility (N,%)			
Dependent	360 (51.7)	94 (25.3)	266 (81.8)
Mobile with aid	212 (30.5)	158 (42.6)	54 (16.7)
Independent (immobile)	124 (17.8)	119 (32.1)	5 (1.5)
ASA			
1	63 (9.1)	9 (2.4)	54 (16.6)
2	348 (50.0)	137 (36.9)	211 (64.9)
3	273 (39.2)	216 (58.3)	57 (17.6)
4-5	12 (1.7)	9 (2.4)	3 (0.9)
Dementia (N,%)	159 (22.8)	153 (41.2)	6 (1.8)
Proxy respondents (N,%)	216 (31.0)	197 (53.1)	19 (5.8)
Type of treatment (N,%)			
Non-operative	21 (3.0)	13 (3.5)	8 (2.4)
Intramedullary fixation	255 (36.6)	162 (43.7)	93 (28.6)
Cannulated Hip Screws	57 (8.2)	23 (6.2)	34 (10.5)
Hemi-arthroplasty	288 (41.4)	157 (42.3)	131 (40.3)
Total hip arthroplasty	75 (10.8)	16 (4.3)	59 (18.2)
Type of fracture (N,%)			
Intracapsular	440 (63.2)	208 (56.1)	232 (71.4)
Extracapsular	256 (36.8)	163 (43.9)	93 (28.6)
Length of hospital stay (mean, SD)	8.28 (5.67)	9.46 (6.79)	6.92 (3.67)
Discharge to home (yes, %)	392 (56.3)	164 (44.2)	228 (70.2)
1-year mortality (N, %)	98 (14.1)	86 (23.2)	12 (3.7)
GFI score (mean, SD)	4.78 (4.12)	8.01 (2.78)	1.09 (1.07)
EQ-5D prefracture utility score (mean, SD)	0.72 (0.28)	0.55 (0.26)	0.91 (0.13)
EQ-5D pre fracture VAS (mean, SD)	69.7 (20.6)	57.6 (17.7)	83.4 (13.6)

[a] Educational level: Low = no diploma, primary education, preparatory secondary vocational education; Middle = university preparatory education, senior general secondary education, senior secondary vocational education and training; High = universities of applied sciences: associate degree or university degree.
Abbreviations: N=number; SD: Standard Deviation; : BMI: body-mass index; ASA: American Society of Anesthesiologists grading; EQ-5D: Euroqol 5 dimensions; VAS: visual analogue scale

The longitudinal association between frailty and HS

There were significant differences in health status between frail and non-frail patients during all follow-up time points (p<0.0001; Figure 2). Prefracture frailty was associated with prefracture HS, adjusted for residential status as a confounder (β-0.29; SE 0.02; p<0.001; 95% CI -0.33 to -0.26).

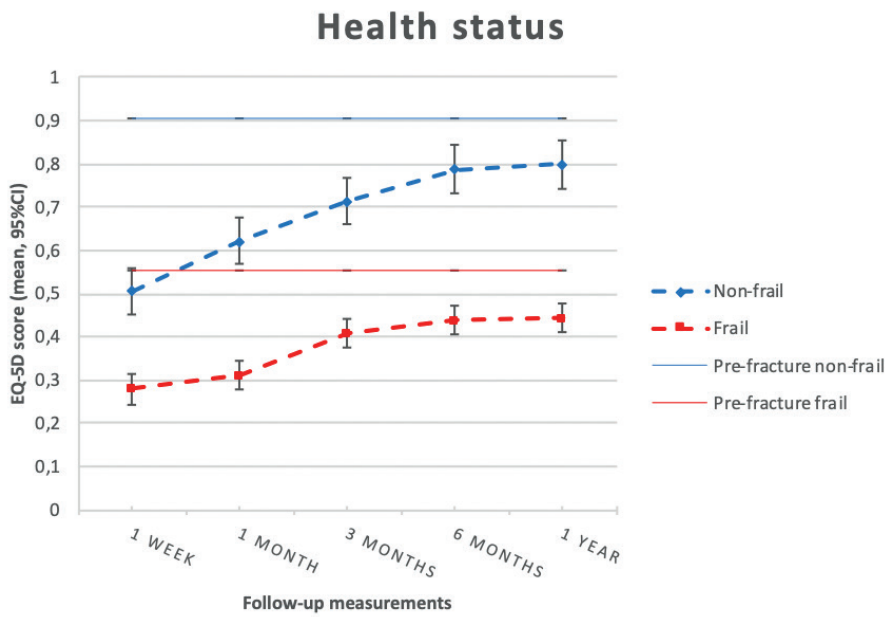

Figure 2. Patterns of health status according to frailty status over time. EQ-5D, EuroQol-5 Dimensions.

The pattern of recovery trajectories in the prevalence of reported problems in the domains of the EQ-5D during the first year period after hip fracture differed between the frail and non-frail patients (Figure 3a/3b). For prefracture, a significantly higher proportion of patients in the frail group had problems with mobility, self-care and usual activities, and experienced more pain and signs of anxiety/depression (p<0.001; Table 2). The percentage of patients with problems of anxiety/depression in the frail group was 54.7% at 1 week and 58.3% at 1 year, compared with 18.9% at 1 week and 14.2% at 1 year in the non-frail group. The aOR of the domain anxiety/depression revealed a 1.346-fold increase in problems (95% CI 1.045 to 1.734) experienced by frail patients over 1 year, compared with the problems in the non-frail group.

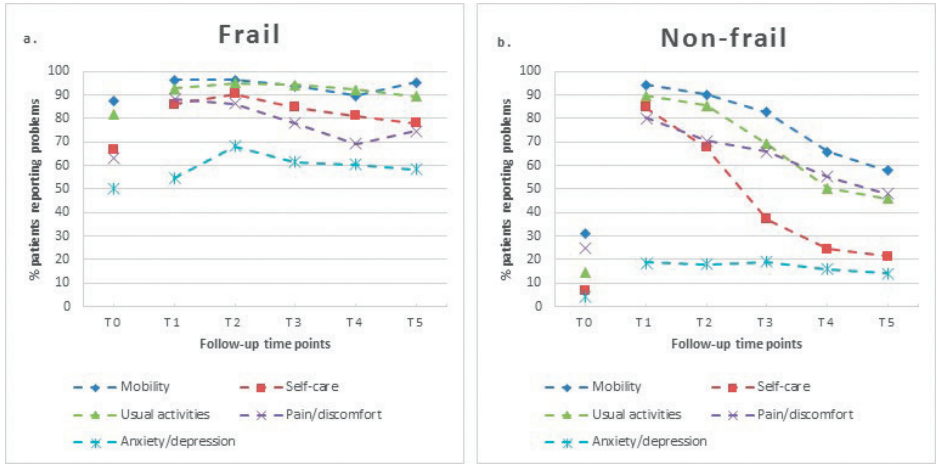

Figure 3. Percentage of frail (a) and non-frail (b) patients reporting problems on each EuroQol-5 Dimensions 3 Level questionnaire item at each follow-up time point.

Table 2. Mixed model analyses of change in EQ-3D-3L for frail patients compared to non-frail patients (=reference group) over time

EQ-5 Domain	Crude			Adjusted[a]		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Mobility	1.970	1.501, 2.590	<0.001	1.186	0.877, 1.605	0.268
Self-care	2.210	1.737, 2.812	<0.001	1.272	0.980, 1.653	0.071
Usual activities	2.545	1.909, 3.393	<0.001	1.165	0.859, 1.579	0.326
Pain/discomfort	1.394	1.089, 1.785	0.008	1.179	0.909, 1.529	0.214
Anxiety/depression	1.928	1.507, 2.468	<0.001	1.346	1.045, 1.734	0.022

Reference group: non-frail
[a] Adjusted for prefracture status of the EQ-5D domain, age, prefracture residential status, ASA and dementia
Abbreviations: EQ: Euroqol; OR: odds ratio; CI: confidence interval

The VIF before the final model analysis ranged from 1.23 to 1.69, indicating that there was no problem with multicollinearity. Frailty was negatively associated with HS (β -0.333; 95% CI -0.366 to -0.299) and self-rated health (β -21.9; 95% CI -24.2 to -19.6) in elderly patients 1 year after hip fracture (Table 3). The estimated crude regression coefficient of -0.333 for frail patients in relation to health status can be interpreted as follows: a patient considered to be frail at baseline has a 0.333 lower EQ-5D utility score compared to non-frail patients. The regression coefficient was -0.115 (95% CI -0.160 to -0.069) for the association between frailty and health status, adjusted for deceased drop-outs and for confounders, including prefracture EQ-5D score, age, prefracture residential status, prefracture mobility, ASA and dementia.

Table 3. Analyses results on the association between frailty and health status/capability wellbeing over 1 year after hip fracture (reference group = non-frail)

	EQ-5D utility score *(health status)*			EQ-VAS *(self-rated health)*			ICECAP-O score *(capability wellbeing)*		
	β	**95% CI**	**p**	**β**	**95% CI**	**p**	**β**	**95% CI**	**p**
Crude	-0.333	-0.366, -0.299	<0.001	-21.90	-24.19, -19.61	<0.001	-0.296	-0.322, -0.270	<0.001
Adjusted[a]	-0.100	-0.143, -0.057	<0.001	-7.74	-10.73, -4.75	<0.001	-0.130	-0.164, -0.096	<0.001
Adjusted[b]	-0.357	-0.392, -0.322	<0.001	-26.40	-29.20, -23.61	<0.001	-0.347	-0.378, -0.316	<0.001
Adjusted[c]	-0.115	-0.160, -0.069	<0.001	-9.42	-13.09, -5.75	<0.001	-0.146	-0.187, -0.106	<0.001

Reference group: non-frail
[a] Adjusted for prefracture EQ-5D utility score, age, prefracture residential status, prefracture mobility, ASA and dementia
[b] Adjusted for death
[c] Adjusted for death, and prefracture EQ-5D utility score, age, prefracture residential status, prefracture mobility, ASA and dementia
Abbreviations: EQ-5D: Euroqol 5 dimensions; EQ-VAS Euroqol Visual Analogue Scale; ICECAP-O: ICEpop CAPability measure for Older People:; Regression coefficient; CI: confidence interval

The longitudinal association between frailty and capability wellbeing

Figure 4 shows differences in capability wellbeing between frail and non-frail patients during all follow-up time points (p<0.0001). We found a significantly strong negative association on average between frailty and capability wellbeing over time, with a death-adjusted regression coefficient that included all confounders of β-0.146 (95% CI -0.187 to -0.106; Table 3).

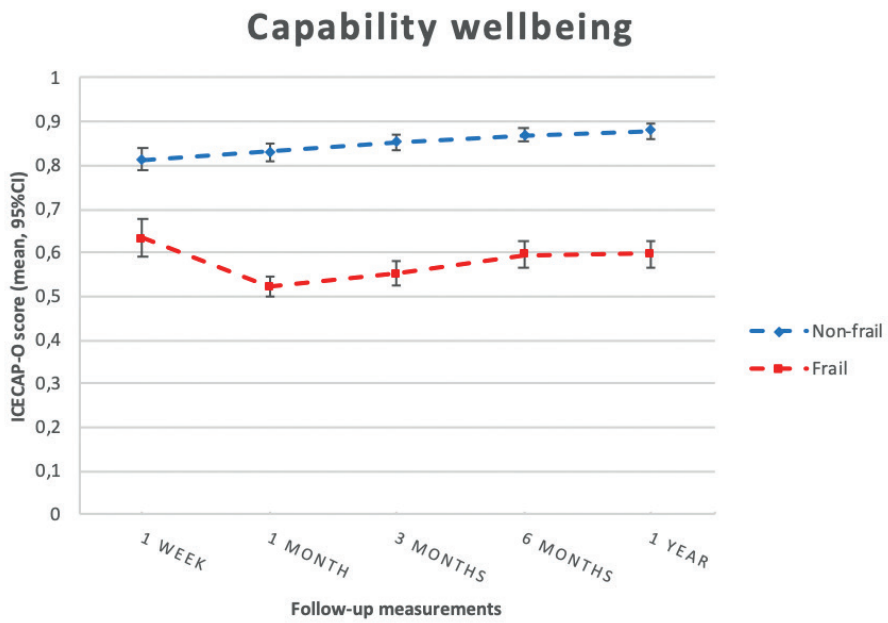

Figure 4. Patterns of capability wellbeing according to frailty status over time. ICECAP-O, ICEpop CAPability measure for Older people.

DISCUSSION

Summary of results

It is well known that elderly patients with a hip fracture have poor QoL[6]. However, it is unknown how much frailty affects patients' QoL. This longitudinal cohort study shows that (i) frail patients with a hip fracture had poorer HS than non-frail patients at baseline, (ii) frail patients had poorer HS and poorer capability wellbeing than non-frail patients over time, and (iii) frailty at the onset of hip fracture was negatively associated with HS and capability wellbeing 1 year after hip fracture. The pattern of recovery trajectories in the prevalence of reported problems in the domains of the EQ-5D during the first year period after hip

fracture differed between the frail and non-frail patients. However, after adjustment for confounders, especially for the concerned prefracture status of the EQ-5D domain, the major differences between frail and non-frail patients disappeared. Confounders, such as prefracture HS, age, prefracture residential status, prefracture mobility, ASA and dementia, weakened also the association between frailty and QoL, but the association remained significant and clinically relevant. Our findings demonstrate that prefracture frailty is significantly associated with poor HS, self-rated health and capability wellbeing the first year after recovery from hip fracture.

Comparison with existing literature

This study demonstrates that frailty is a common condition among elderly patients with a hip fracture. In our study, 53.3% of the patients with a hip fracture were considered frail. This finding is in line with that of a small pilot study of Kistler et al., who found that 51% of patients were considered frail[28]. Previous studies, summarized in a systematic review by Lin and colleagues, showed frailty to be associated with adverse outcomes, such as prolonged length of stay and mortality in older surgical patients[13]. This finding is in line with ours, showing a significant difference in length of stay between frail and non-frail patients (t(696)=-5.845, p<0.001). In line with the findings of Patel et al.[29] and Dayama et al.[30], we also found increased 1-year mortality rates in frail patients with a hip fracture. However, apart from these associations, our results showed that frailty is also negatively associated with QoL. This finding is of major importance because frailty not only seems to influence patients' postoperative outcomes, such as mortality and complications, but also has a perceived impact on the level of patients' physical, emotional and social functioning. In the Netherlands, there is no difference in post-fracture treatments between frail and non-frail patients. However, frail patients have already prefracture more problems with their mobility and selfcare, and therefore, this could have influenced their post-fracture rehabilitation possibilities.

In our study, HS and capability wellbeing do not generally fully recover within 12 months after hip fracture for both frail and non-frail patients. This finding is in line with that of the prospective cohort study of Griffins et al., who also revealed an initial marked decline in HS after hip fracture, followed by improvement within four months and no return to baseline at 1 year after hip fracture[31]. This is also in line with the International Costs and Utilities Related to Osteoporotic fractures Study[32,33]. However, in our study, we showed the pattern of QoL and distinguished

between frail and non-frail patients. We revealed a significantly more prominent decline in HS, self-rated health and capability wellbeing for frail patients compared to non-frail patients the first year of recovery from hip fracture. To show that our findings are clinically relevant, Walters et al. published the minimum clinically important difference of 0.074 for the utility score of the EQ-5D[34].

It is remarkable that in the non-frail group, a high percentage of individuals do not return to prefracture levels within a year on all domains of the EQ-5D. In particular, the domains mobility, pain and usual activities showed major differences between the percentage of non-frail patients and that of frail patients reporting problems at baseline and 1 year after hip fracture . However, the same did not apply to the EQ-5D domain anxiety and depression, which revealed a strong positive association between frailty and anxiety/depression. Until now, the literature revealed a prevalence rate of 10% of patients reporting depressive symptoms after hip fracture[35]. Future research should provide insight into whether frailty is a predictor of psychological distress, characterized by symptoms of anxiety, symptoms of depression and symptoms of posttraumatic stress.

Limitations and strengths

This study had several limitations. First, participants may not accurately recall their status prior to the fracture, which might affect the results of the GFI and the EQ-5D at baseline. To minimize recall bias, the prefracture frailty status and HS data were only collected in patients who flowed into the study until 1 month had passed. In addition, because of the length of the questionnaire, we did not ask the items of the ICECAP-O prior to the fracture, and we could not compare this longitudinal outcome with prefracture capability wellbeing. Second, frail patients showed a higher capability wellbeing score at 1-week follow-up than at 1-month follow-up. This is probably due to selection bias because frail patients in relatively good condition were able to complete the questionnaire at this early follow-up time point. Furthermore, there were more no-show cases in the frail group, resulted in selective drop-out. Therefore, the overall QoL of patients after a hip fracture, especially in the frail group, is probably worse than that presented in this study. On the other hand, an early follow-up time point at 1 week is unique in prospective research in hip fracture populations, and we adjusted for confounding variables in our mixed model analyses. Third, it is well known that surgery for hip fractures is frequently followed by complications[36]. However, information about complications after hip fractures was not collected in this multicenter study, and complications could have affected patients' QoL.

A strength of this study is the setup in the form of a multicenter prospective cohort study. We could include a large number of participants in different geographic locations, along with the possibility of including a wider range of hip-fracture population groups, which increases the generalizability of this study. We also included proxy participants in case a patient was unable to participate in this study for several reasons, including cognitive impairment. Particularly, this group is essential to include in this study because a major proportion of the frail group (41.2%) was suffering from dementia. Gabbe et al. published in trauma patients that differences in HS between patient and proxy respondents showed random variability rather than systematic bias[37]. They concluded that group comparisons using proxy responses are unlikely to be biased. Another strength of this study is that we reported death-adjusted outcomes according to Parsons et al[26]. When reporting QoL for patients after a hip fracture, excluding patients who die during follow-up leads to overly optimistic estimates of patient outcomes and is likely to cause bias.

Implication for clinical practice

The findings of this study support the hypothesis that prefracture frailty has an unfavorable effect on HS, self-rated health and capability wellbeing after a hip fracture. Pre-operative frailty assessment can be valuable in informing patients and their relatives about the impact of hip fracture on patients' physical, emotional and social functioning in the recovery period after a hip fracture. This frailty assessment could classify patients at high risk for unfavorable outcomes regarding poor QoL. It could support clinicians in tailoring treatment for medical decision making at an early phase. A clinically easy-to-use and universal frailty indicator, such as the GFI, could have important implications in prognostic counseling and care planning among older adults with hip fracture.

Conclusions

Our results show that frailty is negatively associated with patients' QoL 1 year after hip fracture, even after adjusting for prefracture HS, age, prefracture residential status, prefracture mobility, ASA and dementia. This study highlights hip fracture as a major cause of burden and morbidity, especially in frail patients. This finding suggests that early identification of prefracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

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SUPPLEMENTAL FILE. GRONINGEN FRAILTY INDICATOR

Physical domain

Are you able to carry out these tasks single handedly and without any help? (The use of help resources, such as a walking stick, walking frame, or wheelchair, is considered to be independent.)

1. Shopping
2. Walking around outside (around the house or to the neighbors)
3. Dressing and undressing
4. Going to the toilet
5. What mark do you give yourself for physical fitness? (scale 0 to 10)
6. Do you experience problems in daily life because of poor vision?
7. Do you experience problems in daily life because of being hard of hearing?
8. Have you lost a lot of weight in the last 6 months? (3 kg in 1 month or 6 kg in 2 months)
9. Do you take 4 or more different types of medicine?

Cognitive domain

10. Do you have any complaints about your memory?

Social domain

11. Do you have ever experienced an emptiness around you?
12. Do you long for other people (to socialize with)?
13. Do you feel abandoned?

Psychological domain

14. In the past 4 weeks, did you feel downhearted or sad?
15. In the past 4 weeks, did you feel anxious or nervous?

Scoring:

Questions 1-4:→Yes = 0; no = 1
Question 5:→0-6 = 1; 7-10 = 0
Questions 6-9:→No = 0; yes = 1
Question 10:→No = 0; sometimes = 0; yes = 1
Questions 11-15:→Yes = 1; sometimes = 1; no = 0

CHAPTER 6

The prevalence and prognostic factors of psychological distress in older patients with a hip fracture: a longitudinal cohort study

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ABSTRACT

Introduction: A hip fracture can be experienced as a traumatic event that can induce psychological distress. The aim of this study is to give more insight into the prevalence of symptoms of psychological distress in older patients following the first year after a hip fracture. In addition, prognostic factors were determined for psychological distress after hip fracture.

Materials and Methods: This hip fracture cohort data was derived from the Brabant Injury Outcome Surveillance, a multicenter longitudinal prospective cohort study. Hip fracture patients (≥65years) admitted to a hospital between August 2015 and November 2016 were asked to complete a questionnaire at 1 week, and 1, 3, 6 and 12 months. The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression and the Impact of Event Scale (IES) was used to assess symptoms of posttraumatic stress (PTS). Prognostic factors were assessed with multivariable logistic mixed models.

Results: In total 570 patients (inclusion rate: 69.7%) were included. The prevalence of psychological distress ranged from 36% at 1 week to 31% at 1 year after hip fracture. Frailty at onset of hip fracture was the most important prognostic factor of symptoms of depression (Odds ratio (OR), 2.74; 95% Confidence interval (CI) 1.41 to 5.34) and anxiety (OR, 2.60; 95% CI 1.15 to 5.85) on average in the year following hip fracture. Frailty was not a prognostic factor of symptoms of PTS (OR, 1.97; 95% CI 0.42 to 9.23).

Conclusions: The prevalence of psychological distress is high in the first year after a hip fracture. Frailty at onset of a hip fracture was the most important prognostic factor of symptoms of depression and anxiety. These findings have important implications for strategies with early identification of frail patients with a hip fracture at high risk of psychological distress.

Keywords: Hip fracture, psychological distress, frailty

INTRODUCTION

Hip fractures are disabling medical events, and associated with a high mortality, loss of independence and reduced quality of life (QoL)[1-3]. A hip fracture can be experienced as a traumatic event, and a substantial proportion of these patients experienced psychological distress[4]. Psychological distress is a general term to describe a state of emotional suffering that interferes with the level of functioning, and could be characterized by symptoms of depression, symptoms of anxiety and symptoms of posttraumatic stress (PTS)[5].

The reported prevalence of depression ranged from 9% and 47% after a hip fracture[6], while the prevalence rates in the general older population are found between 2-10%[7]. High anxiety, history of stressful life events or depression, less satisfaction with subjective support, antidepressant use, being a current smoker, cognitive impairment, pain, and implant type were known as prognostic factors for depressive symptoms[8-10]. Two short-term follow-up studies reported the prevalence of anxiety to be 25% in patients recovery from hip fracture[11,12]. They discovered an association between anxiety, and control beliefs, severe disability and number of severe life events[11,12]. Prevalence of PTS symptoms is found between 3-27% in hip fracture patients and older adults hospitalized for a fall-related-injury[13-15]. Stressful life events experienced during the year before hip fracture and depressive symptoms were prognostic factors for development of PTS symptoms[13]. In addition, female gender, lower level of education, number of comorbid disorders, back/chest injury and current suicidal ideation were already found as prognostic factors for PTS symptoms in older adults hospitalized for fall injury.

The relationship between psychological distress and hip fractures is complex. The presence of psychological distress is associated with an increased risk of mortality, prolonged length of hospital stay, more physical dependence, chance of discharge to a residential or nursing home and uncertain prospects of recovery after a hip fracture[6,16,17]. However, the majority of these studies were based on retrospective-, or cross-sectional- or short-term follow-up data, in a small number of patients. Therefore, we performed a longitudinal prospective cohort study to give more insight into the prevalence of symptoms of psychological distress in older patients during 1 year after hip fracture. In addition, potential prognostic factors including frailty, were determined for explaining variations in psychological distress over time.

MATERIALS AND METHODS

Participants and design

This hip fracture cohort data was derived from the Brabant Injury Outcome Surveillance (BIOS), a multicenter longitudinal prospective cohort study. The BIOS-study protocol has been published[18]. This study was approved by the Medical Ethics Committee Brabant in the Netherlands (project number NL50258.028.14) and performed according to the standards of the Declaration of Helsinki (1964) and its later amendments. This report has been prepared in accordance with the STROBE guidelines[19]. All participants were included between August 2015 and November 2016 from ten hospitals (Noord Brabant, Netherlands) and were invited to participate in the BIOS-study during hospital admission or by post. All included patients provided written informed consent. For all eligible patients it was possible to flow in into the study at two time points, i.e. 1 week and 1 month after hip fracture. Participants were followed up at 3, 6 and 12 months after hip fracture. Patients with a hip fracture being ≥65 years old were included. Exclusion criteria were: (i) patients with cognitive impairment, (ii) pathological hip fractures (iii) and patients with insufficient knowledge of the Dutch language. Cognitive impairment was defined as dementia, based upon history taking from patients or relatives, or a delirium at the time of admission[20].

Data collection

Techniques for longitudinal cohort studies were used to ensure minimum loss to follow-up. Contact addresses, telephone numbers, and email addresses were recorded during enrolment. At the emergency department the participant was given a questionnaire including a pre-paid return envelope. At 1, 3, 6 and 12 months we sent the participant a questionnaire by post or by mail. In case of no return, we endeavored to contact the participant or relative by telephone on several occasions. If this method failed, the participant was considered to be a non-responder at that time point (indicated as 'no show' in Figure 1). Patient characteristics were collected for all patients including age, gender, body mass index (BMI), educational level, prefracture residential status, prefracture mobility, American Society of Anesthesiologists grading (ASA), type of fracture, type of treatment, length of hospital stay (LOS) and discharge location. Prefracture health status (HS) was assessed at 1 week or 1 month after hip fracture with the EuroQol-5D-3L questionnaire (EQ-5D)[21]. This instrument described five health domains related to daily activities: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension consists of a three-

level response: no problems, moderate problems or severe problems. A scoring algorithm is available by which each health status description can be expressed into an overall score using a published utility algorithm for the Dutch population (range 0-1)[22]. The EQ-5D has good measurement properties and is used to measure outcome for patients recovering from hip fracture[23].

Prefracture frailty status was assessed at 1 week or 1 month after hip fracture with the Groningen Frailty Indicator. The GFI is a 15-item self-reported instrument and screens for the loss of functions and resources in four domains of functioning: physical, cognitive, social and psychological[24]. The sum score of the GFI ranges from 0 to 15, with a score of ≥4 indicating frailty. The study of The GFI is a feasible, reliable and valid self-assessment in home-dwelling and institutionalized older people by detecting those at high risk for poor outcome[25].

Outcome measures

Symptoms of anxiety and depression were measured with the Hospital Anxiety Depression Scale (HADS)[26]. The HADS is a 14-item self-report questionnaire, and both anxiety (HADS-A) and depressive (HADS-D) symptoms, were assessed with seven questions with a four-point Likert response scale (0–3). Subscale scores range from 0 to 21. Values ≥8 for one of the subscales are regarded as indicative for symptoms of psychological distress[27]. The HADS is internationally known to be a reliable and valid instrument for screening for symptoms of anxiety and depression in a hospitalized older population[27-29].

The IES was used to assess symptoms of PTS indicative of post-traumatic stress disorder (PTSD). The IES consists of 15 items to measure intrusive re-experiences of the trauma and avoidance of trauma-related stimuli[30]. Intrusion is characterized by intrusive thoughts and images about the event, as well as nightmares and strong waves of feelings. Avoidance is characterized by denial of the consequences of the event, emotional numbness, inhibited behavior or safety behaviors. Subjects were asked to indicate how frequently each of the 15 items were true for them during the past seven days. The IES score using a response scale, consisting of 'not at all', 'rarely', 'sometimes', and 'often', ranging from 0 through 75. An IES score of ≥35 represents symptoms of post-traumatic stress indicative of PTSD. This cut-off score produced a sensitivity of .89, and a specificity of .94 according to the Diagnostic and Statistical Manual of Mental Disords, 4th edition (DSM-IV) criteria for PTSD as the gold standard[31]. The IES has proven to be a clinically valid instrument which is able to discriminate between

people with mild and severe stress reactions in different populations, including people who experienced stressful medical events[32].

Statistical analysis

Descriptive statistics of the cohort were presented as mean with standard deviation (SD) for continuous variables and as numbers and percentages for dichotomous and categorical variables. Missing items of the HADS were first imputed with individual subscale means according to the half-rule (at least half of the items were answered)[33]. Missing baseline characteristics and missing sum scores in HADS and IES were imputed according to multiple imputation, using the multivariate imputation by chained equations (MICE) procedure[34]. The dataset was imputed 15 times with 5 iterations. Patient demographics were compared between responders and non-responders. Prevalence of psychological distress was shown graphically over time. Potential prognostic factors were age, gender, ASA, prefracture residential status, prefracture mobility, type of fracture, LOS, discharge location and frailty status. Collinearity between covariates was tested and there was no assumption of correlated predictors. After univariate analysis with dichotomous outcome (0='no psychological distress' HADS<8 & IES<35 and 1='symptoms of psychological distress'; HADS≥8 and IES≥35), we performed multivariable analysis. Odds ratios (OR) for the prognostic factors on average following 1 year after hip fracture were calculated in a multivariable logistic mixed model, adjusted for prognostic factors. We performed two multivariable adjusted analyses; one with and one without frailty status as potential prognostic factor to reveal the role of frailty in our analysis. Analyses were conducted using SPSS version 24.0 (IBM Statistical Package for Social Sciences, Armonk, NY, USA) and R version 3.4.0 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Study population

Figure 1 shows the flow diagram of study participants. Responders of the questionnaires were significantly younger compared to the non-responders (78.4 [SD: 8.1] and 82.8 [SD: 7.8] years, respectively). Responders were more often healthy (ASA 1 or 2; 70% vs 51%) and had a shorter LOS (mean LOS 8.3 [SD 4.5] vs 9.1 [SD 6.3]) compared to the non-responders. In total 570 patients were included (69.7% inclusion rate) and Table 1 shows baseline patients' characteristics. In total, 264 (46.3%) participants were considered as frail and 21 (3.7%) participants had an early-onset dementia, but were capable (with help) to

complete the questionnaires. In total, 75 responders (16.2%) prefracture reported problems on the EQ-5D anxiety/depression domain.

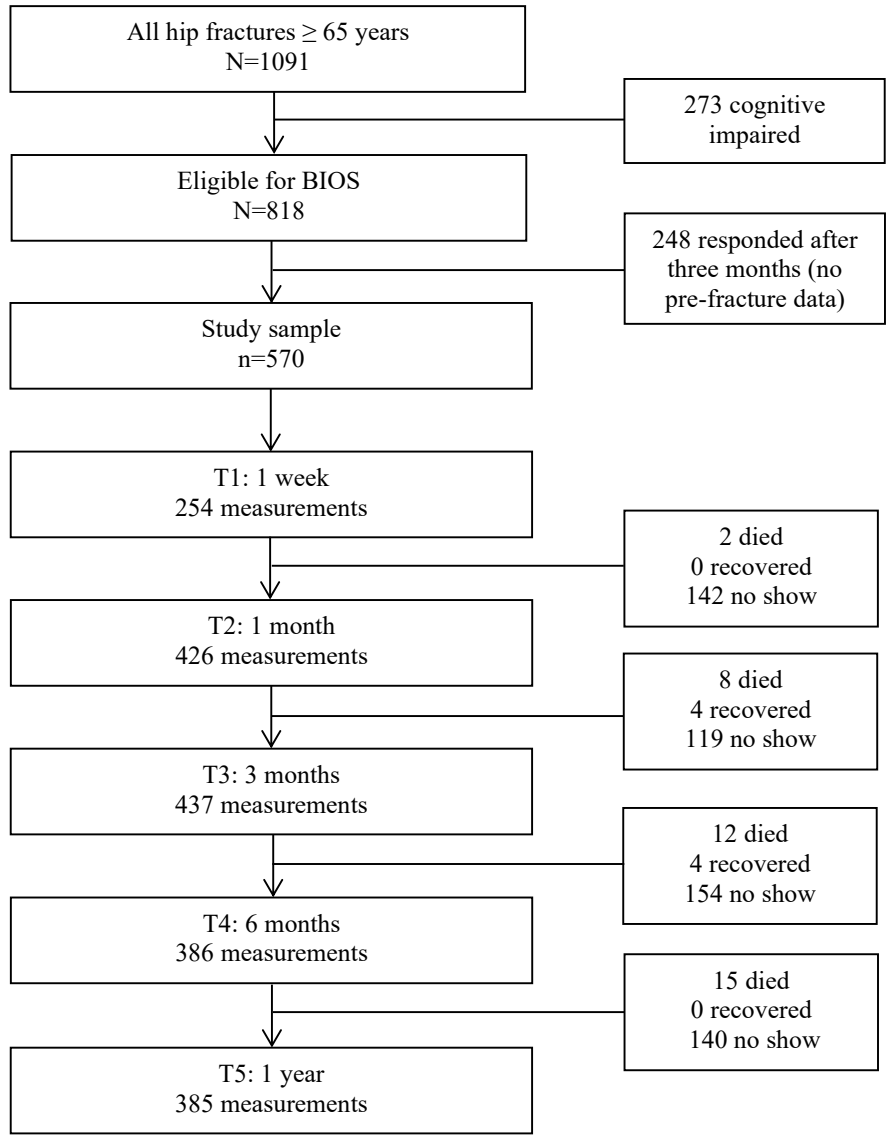


Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'. BIOS, Brabant Injury Outcome Surveillance; T1, 1 week; T2, 1 month; T3, 3 months; T4, 6 months; T5, 1 year

Table 1. Baseline patient characteristics

Characteristic		Sample size (N=570)
Age (mean, SD)	Years	78.4 (8.1)
Sex (N,%)	Female	393 (68.9)
BMI (mean, SD)		25.2 (5.1)
Educational level[a] (N,%)	Low	375 (65.8)
	Middle	100 (17.5)
	High	95 (16.7)
Prefracture residential status (N,%)	Community dwelling	525 (92.1)
	Institution	45 (7.9)
Prefracture mobility (N,%)	Dependent	308 (54.0)
	Mobile with aid	134 (23.5)
	Independent	38 (6.7)
	Unknown	90 (15.8)
ASA	1	63 (11.1)
	2	337 (59.1)
	3	161 (28.2)
	4	9 (1.6)
Frailty status[b]	Yes	264 (46.3)
Dementia[c] (N,%)	Yes	21 (3.7)
Type of fracture N, %)	Intracapsular	376 (66.0)
	Extracapsular	194 (34.0)
Type of treatment (N,%)	Non-operative	13 (2.3)
	Intramedullary fixation	194 (34.0)
	Cannulated Hip Screws	54 (9.5)
	Hemi-arthroplasty	238 (41.8)
	Total hip arthroplasty	71 (12.5)
Length of hospital stay (mean, SD)	Days	8.18 (4.44)
Discharge location[d] (%)	Home	326 (57.2)
	Institution	244 (42.8)
EQ-5D score (mean, SD)		0.82 (0.22)
EQ-VAS (mean, SD)		76.4 (18.54)
EQ-5 Domain anxiety/depression (N,%)[e]	No problems	388 (83.8)
	Moderate problems	65 (14.0)
	Extreme problems	10 (2.2)

[a] Educational level: Low = no diploma, primary education, preparatory secondary vocational education; Middle = university preparatory education, senior general secondary education, senior secondary vocational education and training; High = universities of applied sciences: associate degree or university degree.
[b] assessed with Groningen Frailty Indicator (score ≥ 4 considered as frail)
[c] Early-onset dementia, but patients were capable (with help) to complete the questionnaires
[d] Institution: nursing home or rehabilitation facility
[e] Number of missing values: EQ-5D score: n=90; EQ-5 Domain anxiety/depression: n=107
Abbreviations: BMI body-mass index; ASA, American Society of Anesthesiologists grading; EQ-5D, Euroqol 5 dimensions; VAS: visual analogue scale

Prevalence of psychological distress

Psychological distress was prevalent in 36% (n=92) of the participants at 1 week and in 31% (n=120) at 12 months after hip fracture (Figure 2). Symptoms of depression were prevalent in 29.5% (n=75) at 1 week after hip fracture to 22.6% (n=87) at 1 year after hip fracture. Prevalence of symptoms of anxiety ranged from 21.3% (n=54) to 19.7% (n=76), and symptoms of PTS ranged from 8.7% (n=22) to 10.9% (n=42) during the first year after hip fracture.

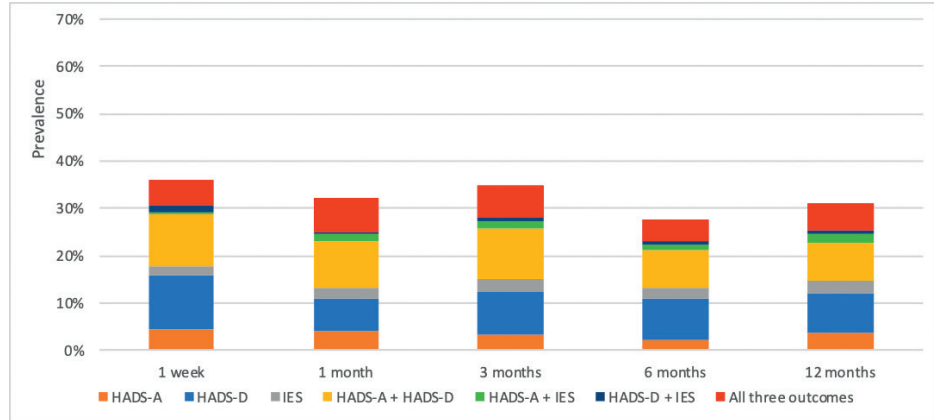


Figure 2. Prevalence of patients with psychological distress (at least one of the outcome measures above cut-off) in the first year after hip fracture, and percentages of co-occurrence of psychological distress

Frailty and psychological distress

Figure 3 shows the prevalence of participants with psychological distress during 12 months after a hip fracture for frail and non-frail patients. Psychological distress was prevalent in 63% of the frail patients and in 22% of the non-frail patients at 1 week after hip fracture. The prevalence of psychological distress was 50% in the frail patients and 19% in the non-frail patients at 12 months after hip fracture. Symptoms of depression were most prevalent in both groups. Multivariable logistic mixed model analyses including frailty indicated that this variable was a prognostic factor of symptoms of anxiety (OR, 2.60; 95% CI 1.15 to 5.85; Table 2) and symptoms of depression (OR, 2.74; 95% CI 1.41 to 5.34; p=0.003; Table 3) on average in the year following fracture. Frailty was no prognostic factor of symptoms of PTS (OR, 1.97; 95% CI 0.42 to 9.23; Table 4).

Table 2. Univariable and multivariable odds ratios with 95% CI for prognostic factors of anxiety measured with HADS-A

Variables	Univariable			Multivariable including frailty			Multivariable excluding frailty		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age ≥ 80 years (ref: <80 years)	5.66	2.23 - 14.33	<0.01	1.79	0.84 - 3.82	0.13	2.01	0.86-4.70	0.11
Female gender (ref: male)	2.79	1.01 - 7.72	0.05	1.50	0.72 - 3.13	0.28	1.95	0.84-4.52	0.12
ASA III/IV/V (ref: I/II)	5.31	1.47 - 19.27	0.01	1.15	0.43 - 3.05	0.78	2.16	0.77-6.02	0.14
Prefracture residential status: institution (ref: community dwelling)	6.40	0.73 - 56.00	0.09	0.81	0.19 - 3.53	0.78	1.28	0.25-6.42	0.77
Prefracture mobility: *(ref: independent)*									
With aid	9.95	3.59 - 27.63	<0.01	0.72	0.30 - 1.74	0.47	2.37	0.93-6.07	0.07
Dependent	36.24	5.90 - 222.82	<0.01	0.59	0.12 - 3.05	0.53	8.24	1.70-39.90	<0.01
Type of fracture: extracapsular (ref: intracapsular)	2.26	0.80 - 6.35	0.12	1.18	0.59 - 2.37	0.63	1.35	0.61-2.98	0.46
Length of hospital stay (days)	1.28	1.15 - 1.42	<0.01	1.07	0.98 - 1.16	0.14	1.09	0.98-1.21	0.12
Discharge location: Institution (ref: home)	8.33	3.54 - 19.60	<0.01	2.15	0.93 - 4.98	0.07	3.26	1.27-8.36	<0.01
Frailty: yes (ref: no)	15.86	7.21 - 34.89	<0.01	2.60	1.15 - 5.85	0.02			

Abbreviations: CI, confidence interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; OR, odds ratio; ASA, American Society of Anesthesiologists grading

Table 3. Univariable and multivariable odds ratios with 95% CI for prognostic factors of depression measured with HADS-D

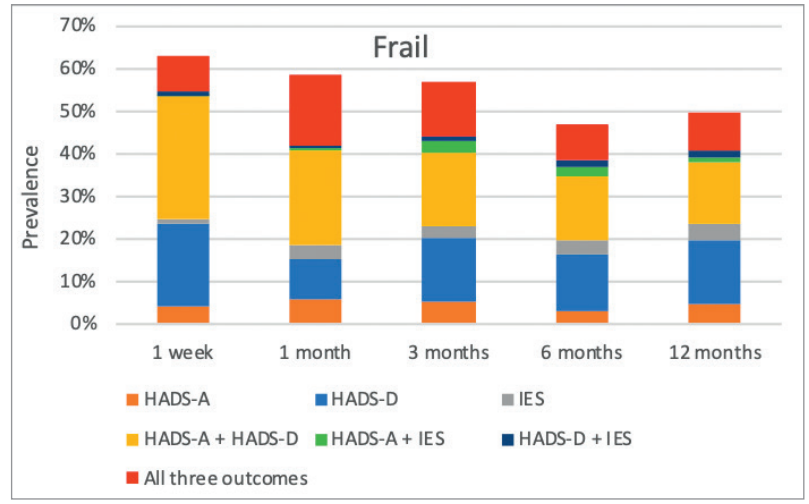
Variables	Univariable			Multivariable including frailty			Multivariable excluding frailty		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age ≥ 80 years (ref: <80 years)	5.75	2.88 - 11.47	<0.01	1.61	0.87 - 2.99	0.13	1.71	0.91-3.23	0.10
Female gender (ref: male)	1.73	0.84 - 3.56	0.14	0.87	0.48 - 1.57	0.63	0.98	0.52-1.85	0.95
ASA III/IV/V (ref: I/II)	11.19	4.75 - 26.38	<0.01	1.97	0.94 - 4.12	0.07	3.45	1.64-7.24	<0.01
Prefracture residential status: institution (ref: community dwelling)	14.70	3.65 - 59.21	<0.01	0.92	0.29 - 2.90	0.88	1.41	0.44-4.53	0.56
Prefracture mobility:									
With aid (ref: independent)	13.97	5.63 - 34.69	<0.01	0.89	0.44 - 1.78	0.73	2.64	1.31-5.30	<0.01
Dependent (ref: independent)	107.89	21.07 - 552.44	<0.01	1.54	0.46 - 5.13	0.48	16.45	5.06-53.43	<0.01
Type of fracture: extracapsular (ref: intracapsular)	2.69	1.32 - 5.46	<0.01	1.50	0.85 - 2.65	0.17	1.60	0.89-2.87	0.12
Length of hospital stay (days)	1.32	1.21 - 1.45	<0.01	1.11	1.04 - 1.20	<0.01	1.13	1.05-1.22	<0.01
Discharge location: Institution (ref: home)	9.65	4.80 - 19.40	<0.01	2.20	1.12 - 4.34	0.02	3.30	1.63-6.71	<0.01
Frailty: yes (ref: no)	24.41	11.52 - 51.71	<0.01	2.74	1.41 - 5.34	<0.01			

Abbreviations: CI, confidence interval; HADS-D, Hospital Anxiety and Depression Scale-Depression; OR, odds ratio; ASA, American Society of Anesthesiologists grading

Table 4. Univariable and multivariable odds ratios with 95% CI for prognostic factors of post-traumatic stress measured with IES

Variables	Univariable			Multivariable including frailty			Multivariable excluding frailty		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age ≥ 80 years (ref: <80 years)	1.76	0.62 - 5.01	0.291	0.94	0.22 - 4.05	0.932	1.014	0.294-3.499	0.983
Female gender (ref: male)	1.57	0.53 - 4.71	0.419	1.42	0.33 - 6.12	0.642	1.521	0.444-5.219	0.504
ASA III/IV/V (ref: I/II)	1.23	0.40 - 3.79	0.719	0.72	0.14 - 3.57	0.684	0.962	0.250-3.703	0.955
Prefracture residential status: institution (ref: community dwelling)	2.50	0.40 - 15.51	0.326	1.72	0.14 - 21.25	0.671	2.028	0.216-19.067	0.536
Prefracture mobility:									
With aid (ref: independent)	2.59	0.73 - 9.20	0.141	1.06	0.20 - 5.74	0.949	1.824	0.485-6.850	0.373
Dependent (ref: independent)	3.14	0.36 - 27.65	0.303	0.64	0.04 - 11.06	0.761	2.171	0.231-20.380	0.497
Type of fracture: extracapsular (ref: intracapsular)	1.09	0.37 - 3.16	0.876	0.83	0.20 - 3.36	0.791	0.866	0.269-2.782	0.808
Length of hospital stay (days)	1.10	0.99 - 1.23	0.082	1.01	0.86 - 1.19	0.890	1.023	0.886-1.182	0.753
Discharge location: Institution (ref: home)	2.59	0.97 - 6.89	0.057	1.83	0.38 - 8.77	0.450	2.082	0.547-7.930	0.282
Frailty: yes (ref: no)	3.67	1.29 - 10.42	0.015	1.97	0.42 - 9.23	0.389			

Abbreviations: CI, confidence interval; IES, Impact of Event Scale; OR, odds ratio;; ASA, American Society of Anesthesiologists grading



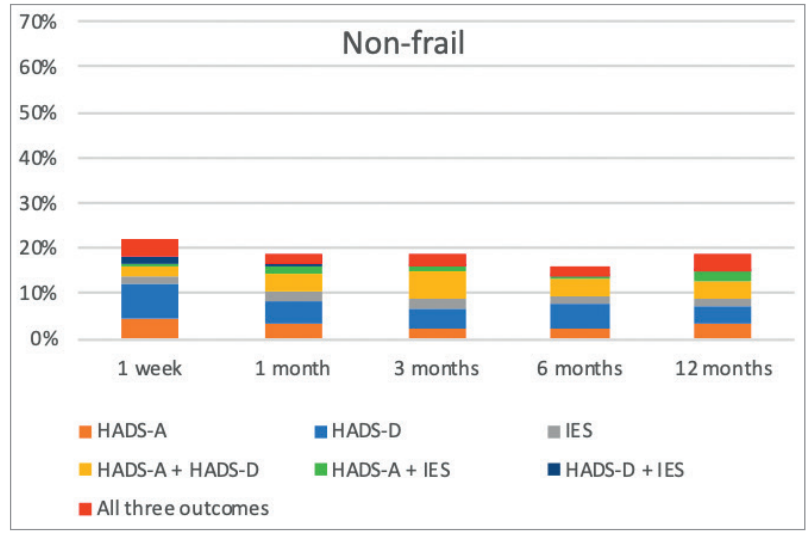


Figure 3. Prevalence of frail and non-frail patients with psychological distress (at least one of the outcome measures above cut-off) in the first year after hip fracture, and percentages of co-occurrence of psychological distress

Prognostic factors for psychological distress

Excluding frailty in our multivariable logistic mixed model analyses showed that dependence in locomotion at baseline and discharge to an institution were prognostic factors for symptoms of anxiety during 1 year after hip fracture (Table 2). Higher ASA scores, dependence in locomotion at baseline, longer LOS at hospital, and discharge to an institution were prognostic factors for symptoms of depression during 1 year after hip fracture (Table 3). In our univariable analyses

frailty is a prognostic factor for symptoms of PTS, however our multivariable analysis showed no prognostic factors for symptoms of PTS (Table 4).

DISCUSSION

Summary of results

This longitudinal cohort study assessed the prevalence and prognostic factors of psychological distress in older patients with a hip fracture. The prevalence of psychological distress was high and ranged from 36% at 1 week to 31% at 1 year after hip fracture. Participants reported most often symptoms of depression, ranged from 29.5% at 1 week after hip fracture to 22.6% at 1 year after hip fracture. Frailty at onset of hip fracture was the most important prognostic factor of symptoms of depression and anxiety on average in the year following hip fracture. No prognostic factors were significantly associated with symptoms of PTS.

Comparison with existing literature

To our knowledge, this is the first study to report the association between frailty and psychological distress in this setting. This study demonstrates that frailty is a prognostic factor of symptoms of anxiety and symptoms of depression. Frailty was already associated with adverse surgical outcomes in geriatric patients, such as in-hospital complications[35], prolonged hospital stay[36,37], adverse discharge disposition[35,36], reduced QoL[38] and mortality[39]. In line with current literature, hip fracture patients are associated with high rates of depressive symptoms[6,9,40,41]. In line with Lenze et al.[9] age and gender was not associated with developing symptoms of depression. In contrast, we found higher ASA scores, prefracture dependence in locomotion and LOS as prognostic factors for developing symptoms of depression, which was in line with others[6,10]. Patients with symptoms of depression were also more significantly discharged to an institution for rehabilitation, which could be related to the findings of Cristancho et al. Patients with depressive symptoms showed poor recovery patterns for mobility[8]. Prefracture, we also found that non-independent ambulators were significant at risk for developing symptoms of depression.

We can compare our findings of anxiety with 1 study, Bond et al[12]. We reported a higher prevalence of anxiety symptoms at 6 months of 16.3%, compared to 10.9%.

Overall, our reported symptoms of PTS ranged from 8.7% to 11.7% following the first 3 months after hip fracture. This is in line with Kornfield et al.[13], but also higher prevalence rates, up to 27% of symptoms of PTS are found[14,15]. This may have been because of differences in assessment methods. We used the IES, to measure symptoms of PTS. Although, this measurement is not designed to diagnose PTSD, because it only consists of two out of three domains (intrusion and avoidance). In clinical practice a structured interview, according to the Statistical Manual for psychiatric Disorders (DSM) could not be used, because this method is too time-consuming. In this study we found no prognostic factors for symptoms of PTS. A possible explanation is the relatively small number of patients experienced symptoms of PTS. Kornfeld et al. concluded that hip fracture is not typically traumatic enough to induce PTSD within 12 weeks in individuals aged 60 and older[13]. However, we revealed especially in frail patients up to 20% experienced symptoms of PTS within 1 year after fracture. We would argue that a hip fracture in those patients is a terrifying event and quite a few patients have symptoms including flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event. Furthermore, the majority of patients with hip fracture experience fear of falling (FoF), which is associated with poor rehabilitation outcomes, diminished QoL, institutionalization and mortality[42-44]. FoF is a potential target for interventions to improve outcome after hip fracture[45]. A significant relationship between FoF and depression, and anxiety in community-dwelling older adults is already known[46]. Therefore, in clinical practice FoF is a crucial factor with components of behavioral avoidance, low self-efficacy and anxiety to address in an early phase after hip fracture.

Strengths and limitations

The first strength of this study is the large number of included patients in this multicenter prospective cohort study. Although inclusion of older patients with a hip fracture is difficult because of the rapid changes in setting (e.g. from hospital to rehabilitation facility to home), we could include a large number of participants in different hospitals with different trauma center levels

The second strength is the use of the HADS, because this measurement does not include items on symptoms that possibly have a physical cause, and is therefore considered unbiased regarding existing medical conditions[47]. It is also a valid instrument with good psychometric properties to measure psychological distress in a population of older people[29].

Third and last strength is that we assessed prefracture reported problems on the EQ-5D anxiety/depression domain. This enabled us to compare the prevalence of symptoms of anxiety and depression with the HADS one year following hip fracture. Because of substantial difference in prevalence before and after hip fracture, the prevalence of psychological distress is related to the hip fracture. Moreover these prevalence rates are much higher than estimates for a general older population[29].

The first limitation in this longitudinal study is attrition bias, because this older population have major disabilities and elevated mortality rates. Besides, older individuals with psychological distress may become particularly unmotivated to participate in research assessments. Therefore our results could be an underestimation of the real prevalence of psychological distress.

Second, the number of patients included in our study at 1 week was relatively small and the percentage of frail patients was relatively lower (34%) as the percentage of frail participants in the study at 3- (42%), 6- (38%) and 12 (40%) months. However, an early follow-up time point at 1 week is unique in prospective research in hip fracture populations, and we adjusted for confounding variables in our mixed model analyses.

Third, personality traits and coping strategies, considered as predictors for psychological distress, were not included in this study and could therefore not be considered as potential prognostic factors.

Last, the GFI includes two questions about the presence of depression and anxiety. Previous research showed that pre-injury psychological distress is an important prognostic factor of psychological distress after injury[48]. However, if only those two questions were positively answered, patients were not yet considered frail. Patients needed at least two more positive answers concerning other domains of functioning, such as physical, cognitive or social[24].

Implication for clinical practice and future research

Gambatesa and colleagues reported in a pilot study that psychological counseling following hip fracture reduced symptoms of anxiety and depression[49]. They suggested to identify ‘low-functioning’ patients, by means of administering QoL, to assess which patients would benefit from counselling. We suggested with our longitudinal data that ‘low functioning’ patients should be classified by

frailty assessment at onset of hip fracture. These two groups, frail and non-frail patients, showed to have different risk profiles for recovery trajectories concerning psychological distress. Mainly, in those frail patients the application of counselling throughout the perioperative period could influence patients’ psychological distress. Patient’s psychological status plays a critical role in treatment after a hip fracture. The treatment does not end after surgical procedure and physical rehabilitation, but reducing psychological distress could improve patients’ outcome concerning pain perception, HS and the mechanisms in FoF[42,45]. However, future studies should investigate the role of treating psychological distress, on reducing the implications of frailty within patients after hip fracture.

Conclusions

In conclusion, the prevalence of psychological distress is high in the first year after hip fracture. Frailty at onset of a hip fracture was the most important prognostic factor of symptoms of depression and anxiety. These findings have important implications for strategies with early identification of frail patients with a hip fracture at high risk of psychological distress.

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PART III

Societal impact

CHAPTER 7

Care-related Quality of Life of informal caregivers of the elderly after a hip fracture

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ABSTRACT

Introduction: Reforms in the Dutch healthcare system in combination with the aging of the population will lead to a strong increase in the demand for informal care in the Netherlands. A hip fracture is one of the most important causes of hospital admissions among frail elderly and informal caregivers experience stress that may have significantly negative impact on the caregivers' Quality of Life. The purpose of the study was to determine the nature, intensity and the care-related Quality of Life (CarerQoL) of informal caregivers of elderly patients in the first 6 months after a hip fracture.

Material and methods: In this cross-sectional study, caregivers of patients with a hip fracture were interviewed about the informal care provided after 1, 3 or 6 months following the injury. The CarerQoL of the informal caregivers was measured with the CarerQoL-7D instrument.

Results: In total, 123 primary informal caregivers were included. The CarerQoL-7D score was on average 83.7 (SD 15.0) after 1, 3 and 6 months, and there were no major differences between the measurement time points. The average amount of informal care provided per patient per week was 39.5 during the first 6 months.

Partners of patients with a hip fracture provided significantly more hours of informal care (β 34.0; 95% CI: 20.9 – 47.1). Female informal caregivers stated a significantly lower level of CarerQoL (β-7.8; 95% CI: -13.3 – 2.3). Female caregivers were 3.0 times more likely to experience relational problems (aOR 3.02; 95% CI 1.08-8.43). Caregivers provided care at 6 months were associated with physical health problems (aOR 2.54; 95% CI 1.05-6.14).

Conclusions: Informal caregivers, especially partners, are faced with providing care of greater intensity to elderly patients during the first 6 months after a hip fracture. The CarerQoL was not associated with the intensity of the provided informal care. However, this study shows that a considerable group of informal caregivers for elderly patients with a hip fracture experienced relational, physical and mental health problems that stemmed from providing intensive informal care during the first 6 months.

Kewords: Hip fracture, Elderly, Informal care, CarerQoL instrument

INTRODUCTION

Due to recent reforms in the Dutch healthcare system, the number of elderly people remaining at home longer continues to rise. By 2020, 800 of the 2000 nursing homes in the Netherlands will be closed due to increasingly stringent cost-containment policies involving the Long-Term Care Act introduced in 2015[1]. The Social Support Act 2015 transferred publicly provided care to the private sector, calling for more self-reliance on the part of citizens and creating a larger role for municipalities in its organization. This led to a reduction in the household support and home care that is provided to patients needing temporary services following hospital discharge, patients with chronic conditions requiring medical services, people with mental or psychological disabilities, and individuals in need of end-of-life care[2,3]. The main goal of these health-care reforms is to keep care affordable and to increase both the system's efficiency and its responsiveness to patient needs. These reforms, in combination with the aging of the population, will lead to a strong increase in the demand for informal care in the Netherlands[4,5].

The current situation shows that informal caregivers are overburdened, and there is increasing awareness that the impact of providing informal care to patients is continuing to grow[6-9]. Earlier research has revealed that informal care affects the well-being of informal caregivers and can lead to personal and social costs. The mortality of older informal caregivers may even increase when they take on the care of their partners[10,11].

In 2014, in the Netherlands, 20,254 patients were admitted to hospital with a hip fracture, 17,184 of whom were 65 years and older[12]. A hip fracture is one of the most important causes of hospital admissions among the elderly and leads to a loss of independence and Quality of Life (QoL), as well as being associated with a high mortality rate[13,14]. Therefore, these patients belong to one of the larger groups in society that suddenly need informal care for a shorter or longer period. The recovery process after treatment depends on several aspects, such as comorbidity, the level of activities of daily living (ADL), living environment, cognitive ability and the psychosocial status of the patient[15]. This process can be slow and difficult for dependent elderly patients, and the role of informal caregivers is very important[16]. Informal caregivers not only provide practical help but also offer emotional and psychological support and have a key role in enhancing patient motivation. However, in-depth interviews with 10 informal caregivers providing care to patients with hip-fractures showed that the new caregiver role can be

overwhelming. Informal care required management of a multitude of caregiving activities, including assistance in physical care, financial transactions, and placement after discharge from the acute hospital. Furthermore, most caregivers must address quickly changing care needs as the care recipients transition from emergency room to operating room, then to a regular hospital unit, followed by a rehabilitation setting, and then home. Most caregivers take up their role without prior knowledge or experience, and the associated stress may have a significantly negative impact on the caregivers' QoL[17].

The main purpose of this study was to determine the nature and intensity of informal caregiving and determine the care-related Quality of Life (CarerQoL) of those providing informal care to elderly patients in the first 6 months after a hip fracture. The second purpose was to examine whether certain informal caregiver or patient characteristics influenced the time investment or CarerQoL of the informal caregiver.

MATERIALS & METHODS

Participants and design

Hip fracture cohort data were derived from the Brabant Injury Outcome Surveillance (BIOS), a prospective cohort study measuring health status (HS) and level of frailty of patients with a hip fracture[18]. One contact person per hip-fracture patient, who was included in the BIOS, was approached by telephone. We used a simple random sampling method where we randomly selected a subset of individuals from the BIOS. Contact persons were approached between January and September 2016 at 1, 3 or 6 months following a hip fracture in their loved ones. It was a cross-sectional study, and all caregivers participated at one time point only. Contact persons, a family member or an unpaid helper, were asked if they provided assistance with personal care, household chores, nursing, mobility outdoors, logistic- or social activities. The Medical Ethics Committee Brabant approved the study (NW2016-26). Informed consent was obtained from all participants. Caregivers were included if they provided informal care to a hip-fracture patient aged 65 years and older at 1, 3 or 6 months. Exclusion criteria were (i) patients who did not receive informal care, (ii) patients for whom no informal caregiver was available and (iii) patients who died before the point of measurement.

Instruments

We obtained patient characteristics from the medical files and the BIOS study. We examined informal caregivers' socio-demographic and health characteristics through a telephone interview. Informal caregivers' socio-demographic and health characteristics included age, sex, relationship to the patient, educational attainment, and nature and intensity of the informal care they had provided.

CarerQoL – The care-related Quality of Life instrument (CarerQoL-7D) was conducted by a telephone interview and measured CarerQoL in terms of subjective burden and general well-being (supplemental file)[19]. This questionnaire consists of the CarerQoL-7D and the CarerQoL-VAS (visual analogue scale). The CarerQoL-7D consists of seven items, each covering one dimension of the subjectively experienced impact of informal care (satisfaction, support, problems with daily activities, and financial, relational, mental health and physical health problems). Informal caregivers can indicate for each dimension whether they had experienced 'no' problems, 'some' problems or 'a lot' of problems. The scores were transformed to a scale of 0 (worst informal care situation) to 100 (best informal care situation) using the Dutch CarerQol tariff, in which a higher score represents a better CarerQoL[20]. The CarerQoL-VAS, from 0 (completely unhappy) to 10 (completely happy), measured general well-being in terms of happiness. A second VAS (CarerQoL-VAS 'transfer') was added, and informal caregivers were asked to estimate their general well-being in the hypothetical situation that all informal care activities were to be passed on to another, self-selected person. We calculated the difference between these VAS scores to explore whether informal caregivers derived happiness from providing informal care (so-called process utility). The construct validity of the CarerQoL-7D instrument was validated in different study settings (i.e., the general population, hospitals, long-term care facilities and primary care centers)[21-23].

EQ-5D – The Euroqol-5 Dimensions using 3 levels (EQ-5D) was used in the BIOS to measure HS of the hip-fracture patient[24]. This generic health utility instrument consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 levels each (none, some or many limitations). The Dutch tariff was used to obtain utilities [25,26]. The EQ-5D is a valid and reliable instrument and can be used as an outcome measure for patients recovering from a hip fracture[25-27].

GFI – The Groningen Frailty Index (GFI) was used in the BIOS to evaluate the level of frailty of the patient[28-30]. The GFI is a 15-item self-reported instrument and measures the loss of functions and capabilities in four domains: physical, cognitive, social and mental functioning. The sum score of the GFI ranges from 0 to 15, with a score of ≥4 indicating frailty. The GFI is a valid, reliable and feasible instrument for use with elderly people living either at home or in an institution to detect those who are at a high risk of a poor outcome[29,30].

Data analysis

We calculated descriptive statistics to assess caregivers' and patients' characteristics. We expressed continuous variables as a mean with standard deviation and categorical variables as numbers and percentages. We described the nature and intensity of informal care provided by caregivers, as expressed by hours of care per week and types of activities. We evaluated the CarerQoL-7D score, CarerQoL-VAS, CarerQoL-VAS 'transfer' and process utility at 1, 3 and 6 months. We used univariate linear regression analysis to assess whether caregivers' or patients' characteristics influenced the intensity of informal care or the CarerQoL of the informal caregiver. We built a multivariable linear regression model to determine the association between independent caregivers' and patients' characteristics and dependent variables, intensity of provided informal care and CarerQoL of the informal caregiver, adjusted for different covariates. Different covariates were clinically relevant variables from both caregivers' and patients' characteristics, such as hours of informal care, partner, caregiver age, caregiver sex, caregiver educational attainment, patient age, living in an institution, dementia and measurement time points. Finally, we built a multivariable logistic regression model to examine how caregivers' and patients' characteristics are associated with the dimensions of the CarerQol-7D, adjusted for the covariates partner, caregiver age, caregiver sex, living in an institution, dementia and GFI. Regression coefficients (β), adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated. All analyses were conducted with SPSS version 24 (IBM SPSS Statistics for Windows, Armonk, NY, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

Response

In total, 255 contact persons for patients with a hip fracture were approached by telephone. Forty-nine persons were excluded; of thee, 29 contact persons

stated that they had never had to provide informal care, in 11 cases no informal caregiver was available, and nine patients had passed away by the time of the call. In total, 206 caregivers were eligible for inclusion. A total of 78 persons could not be reached, despite repeated telephone calls, and five caregivers expressed no interest. No significant difference was found in patient demographics (age: p=0.29; sex: p=0.63) between responders and non-responders. Table 1 provides caregiver and patient characteristics for the study population. In total, 123 informal caregivers who provided informal care to 123 hip fracture patients were included. (response: 59.7%). Forty, 39 and 44 informal caregivers were included, respectively, in the groups approached at 1, 3 or 6 months after a hip fracture was suffered by their loved one. The mean age of the caregivers was 64.6 years and 55.3% were female. The patients' mean age was 79.9 years, and 74.0% were female. Patients had a mean total GFI score of 10.7 and were all considered to be frail. In the group of caregivers providing informal care at 1 month after hip fracture, there were no patients with dementia or patients who, prefracture, were living in an institution.

Table 1. Characteristics of informal caregivers and patients after a hip fracture

	Total (n=123)	1 month (n=40)	3 months (n=39)	6 months (n=44)
Caregiver characteristic				
Age in years (M,SD)	64.6 (12.2)	67.6 (11.0)	64.7 (12.2)	61.9 (12.9)
Female gender (N,%)	68 (55.3)	22 (55)	22 (56.4)	24 (54.5)
Relationship (N,%)				
Partner	55 (44.7)	27 (67.5)	15 (38.5)	13 (29.5)
Child	53 (43.1)	9 (22.5)	20 (51.3)	24 (54.5)
Sibling	7 (5.7)	2 (5.0)	2 (5.1)	3 (6.8)
Other	8 (6.5)	2 (5.0)	2 (5.1)	4 (9.1)
Educational attainment[a] (N,%)				
Low	37 (30.1)	11 (27.5)	15 (38.5)	11 (25)
Middle	56 (45.5)	21 (52.5)	15 (38.5)	20 (45.5)
High	30 (24.4)	8 (20.0)	9 (23.0)	13 (29.5)
Patient characteristic				
Age in years (M,SD)	79.9 (8.3)	77.6 (8.1)	79.3 (8.7)	82.6 (7.3)
Female gender (N,%)	91 (74.0)	27 (67.5)	29 (74.4)	35 (79.5)
Dementia; yes (%)	22 (17.9)	0 (0.0)	8 (20.5)	14 (31.8)
Pre-fracture living in an institution	17 (13.8)	0 (0.0)	5 (12.8)	12 (27.3)
Discharge to home[b]; yes (%)	59 (55.7)	22 (75.9)	18 (48.6)	19 (47.5)

Table 1. Continued.

	Total (n=123)	1 month (n=40)	3 months (n=39)	6 months (n=44)
Pre-fracture mobility[b] (N,%)				
Freely mobile without aids	57 (54.8)	27 (75.0)	18 (51.4)	12 (36.4)
Mobile with aids	44 (42.3)	9 (25.0)	16 (45.7)	19 (57.6)
No functional mobility	3 (2.9)	0 (0.0)	1 (2.9)	2 (6.0)
Type of treatment (N,%)				
Nonoperative	2 (1.6)	1 (2.5)	1 (2.6)	0 (0.0)
Intramedullary fixation	47 (38.2)	11 (27.5)	19 (48.7)	17 (38.6)
Cannulated screws	12 (9.8)	6 (15.0)	5 (12.8)	1 (2.3)
Hemi-arthroplasty	49 (39.8)	17 (42.5)	10 (25.6)	22 (50.0)
Total hip arthroplasty	13 (10.6)	5 (12.5)	4 (10.3)	4 (9.1)
Length of hospital stay (M,SD)	8.6 (5.0)	7.3 (3.6)	9.5 (5.7)	9.0 (5.3)
Comorbidity				
None	19 (15.4)	10 (25.0)	4 (10.3)	5 (11.4)
One	45 (36.6)	12 (30.0)	17 (43.6)	16 (36.4)
Two or more	59 (48.0)	18 (45.0)	18 (46.2)	23 (52.3)
Post-fracture mobility (N,%)				
Freely mobile without aids	17 (13.8)	1 (2.5)	6 (15.4)	10 (22.7)
Mobile with aids	84 (68.3)	27 (67.5)	28 (71.8)	29 (65.5)
No functional mobility	22 (17.9)	12 (30.0)	5 (12.8)	5 (11.4)
EQ-5D (M,SD)	0.53 (0.27)	0.57 (0.26)	0.52 (0.28)	0.50 (0.28)
GFI (M,SD)	10.7 (2.9)	9.8 (1.8)	9.9 (2.3)	12.3 (3.3)

[a] Educational attainment: Low = no diploma, primary education, preparatory secondary vocational education; Middle = university preparatory education, senior general secondary education, senior secondary vocational education and training; High = universities of applied sciences: associate degree or university degree.
[b] Number of missing values: discharge to home: n=17; pre-fracture mobility: n=19
Abbreviations: M = mean; SD = standard deviation; n = number of caregivers; EQ-5D = Euroqol-5 Dimensions; GFI = Groningen Frailty Indicator

Intensity

On average, informal caregivers provided 39.5 hours (SD 32.8) of informal care per week for the first 6 months after a hip fracture, which differed significantly between the measurement time points (p≤0.01). At 1, 3 and 6 months after the hip fracture, this figure was 50.3 (SD 32.1), 45 (SD 38.2) and 25 (SD 21.7) hours per week, respectively (Table 2). Around half of the informal care activities consisted of providing additional social support, and approximately 20% of the activities involved carrying out household chores.

Table 3 shows the univariate and multivariable linear regression analysis. Univariate analysis shows that caregiver characteristics such as being a partner (β 42.5) age (β 1.3) and educational attainment (middle vs. low β-17.0 and high vs. low β-27.4) were significantly associated with the intensity of informal care provided. Patient characteristics such as age (β-1.4), living in an institution (β -20.6), dementia (β-21.5) and GFI (β-2.9) were also significantly associated with intensity of informal care provided. In the multivariable analyses, the intensity of care provided was not significantly explained by patient or caregiver characteristics, except for the relationship with the patient: if the informal caregiver was the patient's partner, the intensity of informal care was 34.0 hours per week higher over the first 6 months after hip fracture compared to a non-partner (95% CI 20.9-47.1).

Table 2. Intensity of informal care provided by nature of care for hip fracture patients and CarerQoL-score

	Total (n=123)	1 month (n=40)	3 months (n=39)	6 months (n=44)	p
Total hours per week of informal care (M,SD)	39.5 (32.8)	50.3 (32.1)	45.0 (38.2)	24.8 (21.7)	<0.01
Nature of informal care activities *(% of total hours)*					
- Personal care	8.6	9.1	9.4	6.3	
- Household chores	19.7	20.1	18.7	20.5	
- Nursing	1.4	3.1	0.2	0	
- Mobility outdoors	9.1	7.7	7.9	13.5	
- Logistic activities	4.5	2.8	4.4	7.7	
- Social activities	56.8	57.2	59.4	52.0	
CarerQoL-7D score (M,SD)	83.7 (15.0)	81.6 (16.7)	87.0 (12.8)	82.6 (15.0)	0.23
CarerQoL-VAS (M,SD)	7.6 (1.5)	7.3 (1.8)	7.9 (1.1)	7.5 (1.3)	0.13
CarerQoL-VAS 'transfer' (M,SD)	6.8 (2.1)	6.5 (2.0)	6.7 (2.4)	7.2 (1.9)	0.26
Process utility (M,SD)	0.7 (2.0)	0.8 (2.0)	1.2 (2.3)	0.27 (1.71	0.11

Abbreviations: M = mean; SD = standard deviation; n = number of caregivers

Table 3. Univariate- and multivariable linear regression results for association with intensity of provided informal care of informal caregivers

	Unadjusted[a]			Adjusted[b]		
	β	95% CI	p	β	95% CI	p
Caregiver characteristic						
CarerQoL	-0.1	-0.5 – 0.3	0.60	-0.2	-0.5 – 0.1	0.19
Partner	42.5	33.4 – 51.5	<0.001	34.0	20.9 – 47.1	<0.001
Age	1.3	0.9 – 1.7	<0.001	0.3	-0.2 – 0.8	0.23
Female gender	-11.8	-23.5 – -0.2	0.05	-4.6	-13.8 – 4.7	0.33
Educational attainment						
Middle vs. low	-17.0	-30.2 – -3.8	0.01	-2.4	-13.5 – 8.6	0.66
High vs. low	-27.4	-42.7 – -12.1	0.001	-9.1	-21.9 – 3.6	0.16
Measurement time point						
At 3 months vs. 1 month	-5.4	-19.2 – 8.5	0.45	6.7	-4.9 – 18.4	0.26
At 6 months vs. 1 month	-25.6	-39.0 – 12.1	<0.001	-8.3	-20.1 – 3.5	0.16
Patient characteristic						
Age	-1.4	-2.1 – -0.7	<0.001	0.02	-0.7 – 0.7	0.95
Female gender	-2.0	-15.4 – 11.4	0.77	8.9	-1.7 – 19.5	0.10
Mobility						
Some problems vs. no problems	12.0	-5.2 – 29.2	0.17	2.7	-10.8 – 16.1	0.39
Confined to bed vs. no problems	19.0	-1.8 – 39.9	0.07	5.1	-11.7 – 21.9	0.60
Living in an institution	-20.6	-37.2 – -3.9	0.02	-0.3	-20.8 – 21.5	0.97
Dementia	-21.5	-36.4 – -6.6	<0.01	-7.0	-26.5 – 12.6	0.48
GFI	-2.9	-5.1 – -0.6	0.01	1.9	-0.4 – 4.1	0.10
EQ-5D	10.9	-16.6 – 38.4	0.43	-10.4	-32.2 – 11.4	0.35

[a] Univariate linear regression analysis

[b] Multivariable linear regression analysis, adjusted for: partner, caregiver age, caregiver gender, caregiver educational attainment, patient age, living in an institution, dementia and measurement time points

Abbreviations: CI = confidence interval; CarerQoL = care-related quality of life; EQ-5D = Euroqol-5 Dimensions; GFI = Groningen Frailty Indicator

CarerQoL and process utility

The CarerQoL-7D score was averaged over three measurement time points, 83.7 (SD 15), and did not show any significant differences between the different time points (Table 2). Informal caregivers estimated their general well-being at 7.6 (1.5) on average on the CarerQoL-VAS (Table 2). The CarerQoL-VAS 'transfer' was significantly lower (p<0.001) with an average of 6.8 (2.1), which meant that the process utility measured for the 123 informal caregivers was positive; informal caregivers derive happiness from providing care and would be unhappier if care was transferred to another person. In total, 31.1% had a positive, 48.4% a neutral and 20.5% a negative process utility. No significant differences between the measurement time points were noted for process utility (p=0.11). Figure 1 shows the distribution of responses across the seven domains of the CarerQoL-7D. Almost all the informal caregivers stated that they gained some or a lot of satisfaction from providing informal care (irrespective of time point). The majority did not experience financial problems due to caregiving. At 1, 3 and 6 months, 42.5%, 25.6% and 47.5%, respectively, experienced some to a lot of physical health problems. Some to a lot of mental problems occurred in 30%, 25.6% and 34.1% of caregivers, respectively. In addition, 47.5%, 38.5% and 40.9% reported some to a lot of problems with combining informal care and their own daily activities for the three time points. Informal caregivers who provided more hours of informal care complained significantly more often about physical health problems (p=0.01). Most of the informal caregivers received some or a lot of support from others in providing informal care.

Table 4 shows that female informal caregivers (55.3%) had a significantly lower CarerQoL-7D score in both uni- and multivariable regression analysis (adjusted β-7.8; 95% CI: -13.3 – -2.3). Multivariable linear regression showed no other significant characteristics associated with the CarerQoL-7D score. Caregiver characteristics including age and female sex were associated with relational problems (Table 5). In multivariable models, female caregivers were 3.0 times more likely to experience relational problems (aOR 3.02; 95% CI 1.08-8.43). Caregivers providing care at 6 months were associated with physical health problems (aOR 2.54; 95% CI 1.05-6.14). Dementia was also associated with relational problems (aOR 8.25; 95% CI, 1.35-50.48).

Table 4. Univariate- and multivariable linear regression results for association with CarerQoL of informal caregivers

	Unadjusted[a]			Adjusted[b]		
	β	95% CI	p	β	95% CI	p
Caregiver characteristic						
Hours of informal care	-0.02	-0.1 – 0.06	0.60	-0.05	-0.1 – 0.06	0.38
Partner	0.5	-4.9 – 5.9	0.85	5.3	-3.3 – 13.9	0.23
Age	0.0	-0.2 – 0.2	0.97	0.02	-0.2 – 0.3	0.91
Female gender	-7.1	-12.4 – -1.9	0.01	-7.8	-13.3 – -2.3	0.01
Educational attainment						
Middle vs. low	4.9	-1.3 – 11.2	0.12	5.8	-0.7 – 12.3	0.08
High vs. low	5.3	-1.9 – 12.6	0.15	5.5	-2.1 – 13.1	0.16
Measurement time point						
At 3 months vs. 1 month	5.4	-1.2 – 12.1	0.11	6.3	-0.3 – 12.9	0.06
At 6 months vs. 1 month	1.0	-5.4 – 7.4	0.76	0.6	-6.2 – 7.4	0.86
Patient characteristic						
Age	-0.04	-0.4 – 0.3	0.82	-0.2	-0.5 – 0.2	0.36
Female gender	3.2	-2.9 – 9.3	0.30	1.4	-4.8 – 7.7	0.65
Mobility						
Some problems vs. no problems	4.0	-3.9 – 11.9	0.32	5.4	-2.4 – 13.3	0.17
Confined to bed vs. no problems	5.8	-3.7 – 15.4	0.23	8.3	-1.5 – 18.1	0.10
Living in an institution	3.3	-4.4 – 11.0	0.40	3.8	-4.3 – 11.9	0.36
Dementia	0.4	-6.6 – 7.4	0.91	-0.04	-7.6 – 7.5	0.99
GFI	-0.9	-2.0 – 0.13	0.09	-0.4	-1.6 – 0.9	0.57
EQ-5D	3.0	-8.4 – 14.5	0.60	2.9	-9.1 – 14.9	0.63

[a] Univariate linear regression analysis

[b] Multivariable linear regression analysis, adjusted for: hours of informal care, caregiver age, caregiver gender, caregiver educational attainment, patient age and measurement time points

Abbreviations: CarerQoL = care-related quality of life; CI = confidence interval; EQ-5D = Euroqol-5 Dimensions; GFI = Groningen Frailty Indicator

Table 5. Multivariable logistic regression results for association of dimensions of the CarerQol of informal caregivers

	Adjusted Odds Ratio (95% CI)[a]					
	Fulfillment[b]	Support[b]	Relational problems[c]	Mental health problems[c]	Problems with daily activities[c]	Physical health problems[c]
Caregiver characteristic						
Hours of informal care	1.00 (0.98 – 1.01)	1.00 (0.98 – 1.01)	1.00 (0.98 – 1.03)	1.01 (0.99 – 1.03)	1.02 (1.00 – 1.03)	1.01 (1.00 – 1.03)
Hours of informal care						
>25 hours	1.61 (0.59 – 4.43)	0.92 (0.35 – 2.41)	2.13 (0-.61 – 7.43)	3.43 (1.10 – 10. 64)	1.24 (0.47 – 3.30)	1.62 (0.61 – 4.29)
>40 hours	1.10 (0.37 – 3.30)	1.07 (0.38 – 3.03)	3.00 (0.68 – 13.35)	3.17 (0.82 – 12.27)	2.26 (0.74 – 6.92)	1.77 (0.62 – 5.05)
Partner	1.06 (0.39 – 2.87)	1.82 (0.74 – 4.48)	0.41 (0.13 – 1.28)	0.42 (0.15 – 1.17)	1.24 (0.50 – 3.06)	2.30 (0.92 – 5.73)
Age	0.98 (0.94 – 1.03)	0.99 (0.96 – 1.03)	1.07 (1.01 – 1.12)	1.02 (0.97 – 1.06)	1.00 (0.96 – 1.04)	1.00 (0.96 – 1.04)
Female gender	0.43 (0.18 – 0.98)	0.87 (0.40 – 1.88)	3.02 (1.08 – 8.43)	1.61 (0.67 – 3.85)	1.86 (0.84 – 4.12)	0.96 (0.43 – 2.12)
Educational attainment						
Low	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Middle	1.29 (0.51 – 3.27)	0.78 (0.32 – 1.91)	0.81 (0.26 – 2.51)	0.80 (0.29 – 2.17)	0.78 (0.31 – 1.99)	0.49 (0.20 – 1.23)
High	2.27 (0.72 – 7.21)	0.72 (0.25 – 2.07)	1.12 (0.30 – 4.11)	0.50 (0.14 – 1.72)	2.06 (0.71 – 6.01)	0.45 (0.15 – 1.35)
Measurement time point						
1 month	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
3 months	0.62 (0.37 – 1.04)	1.36 (0.53 – 3.50)	0.75 (0.20 – 2.78)	0.73 (0.25 – 2.17)	0.83 (0.36 – 1.88)	0.48 (0.20 – 1.14)
6 months	0.80 (-.33 – 1.90)	0.85 (0.32 – 2.30)	1.58 (0.46 – 5.46)	0.92 (0.31 – 2.73)	0.78 (0.33 – 1.83)	2.54 (1.05 – 6.14)
Patient characteristic						
Age	1.00 (0.94 – 1.06)	0.97 (0.92 – 1.03)	0.99 (0.92 – 1.06)	0.97 (0.91 – 1.04)	0.99 (0.94 – 1.05)	1.06 (1.01 – 1.13)
Female gender	1.18 (0.46 – 3.00)	1.02 (0.42 – 2.48)	0.29 (0.10 – 0.90)	0.80 (0.30 – 2.19)	0.54 (0.21 – 1.34)	1.43 (0.55 – 3.75)
Mobility						
No problems	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Some problems	0.80 (0.06 – 10.87)	0.88 (0.29 – 2.67)	0.56 (0.16 – 1.95)	0.44 (0.14 – 1.37)	1.80 (0.55 – 5.78)	2.39 (0.68 – 8.41)
Confined to bed	2.71 (0.40 – 18.57)	1.24 (0.33 – 4.65)	0.31 (0.06 – 1.72)	0.22 (0.05 – 1.01)	1.23 (0.30 – 5.04)	1.63 (0.37 – 6.89)

Table 5. Continued.

	Adjusted Odds Ratio (95% CI)[a]					
	Fulfillment[b]	Support[b]	Relational problems[c]	Mental health problems[c]	Problems with daily activities[c]	Physical health problems[c]
Living in an institution	7.00 (0.76 – 64.61)	1.72 (0.28 – 10.51)	0.56 (0.07 – 4.47)	0.31 (0.04 – 2.34)	0.21 (0.03 – 1.58)	0.78 (0.10 – 6.06)
Dementia	0.63 (0.12 – 3.38)	1.27 (0.26 – 6.21)	8.25 (1.35 – 50.48)	0.74 (0.13 – 4.13)	2.71 (0.47–15.69)	0.45 (0.08 – 2.73)
GFI	1.01 (0.85 – 1.19)	0.96 (0.82 – 1.12)	1.08 (0.90 – 1.29)	1.22 (1.03 – 1.46)	1.14 (0.98 – 1.34)	1.14 (0.97 – 1.35)

[a] Adjusted for: partner, caregiver age, caregiver gender, living in an institution, dementia and GFI
[b] Fulfilment and support related to providing care, with contrast between caregivers who rated the level of fulfilment and support of no or some vs caregivers who indicated a lot fulfilment and support.
[c] Relational problems, mental health problems, problems with daily activities, physical health problems, with contrast between caregivers who rated the level of no problems vs caregivers who indicated some or a lot problems.
Abbreviations: CarerQoL = care-related quality of life; CI = confidence interval; GFI = Groningen Frailty Indicator
Note: due to small numbers of caregivers experienced financial problems, no associations within this domain were given in this table.

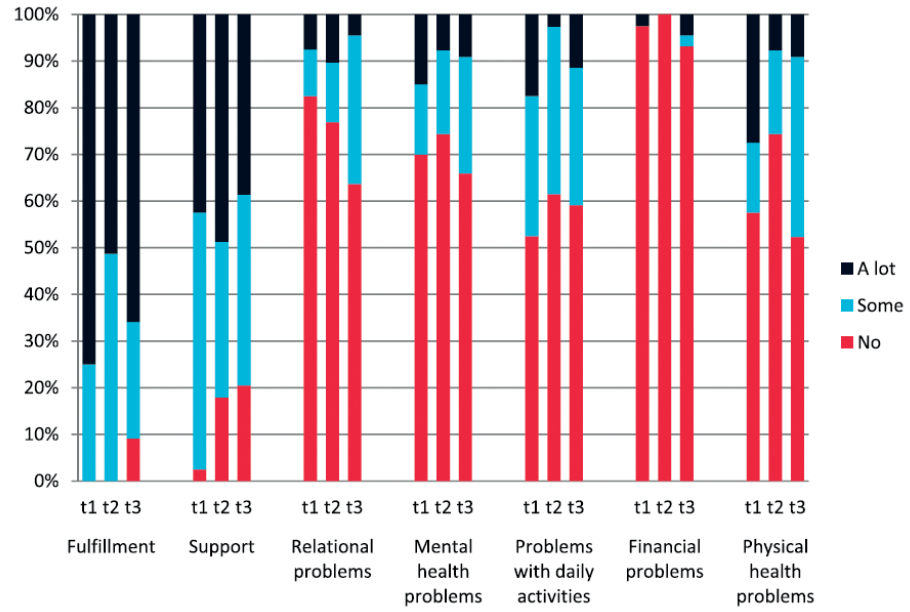

Figure 1. Distribution of CarerQoL-7D – dimensions reported by informal caregivers providing informal care at 1, 3 and 6 months (t1,t2,t3) after hip fracture

DISCUSSION

To our knowledge, this is the first study to examine CarerQoL in informal caregivers of patients aged 65 years and older after a hip fracture. We used the CarerQoL-7D, which characterizes burden across seven dimensions of burden with individual weighted scores.

Our findings contribute important insight regarding the 'invisible work' of managing care during the first 6 months after the hip fracture of a loved one, confirmed by the great intensity of provided informal care with a mean of 39.5 hours per week. This study identifies higher-intensity caregivers, who are largely unrecognized in our healthcare system. Partners provided significantly more hours of informal care per week compared to other types of caregivers, but they showed no difference in CarerQoL-scores (β 4.3; 95% CI -3.3-13.9).

The median CarerQoL-7D score (83.7) found in this study is similar to that in earlier CarerQoL-7D studies[31,32]. Hoefman et al. and Van Dam and colleagues examined the CarerQoL (79.1 and 83.9, respectively) of informal caregivers

in a heterogeneous patient population that was representative of the Dutch population. Our finding confirms the assumption that there is no significant association between age and CarerQoL of the informal caregiver. In contrast to our study, they revealed a significant association between patients with impaired cognition and a lower CarerQoL-score. However, when focused on the domain 'relational problems', we found a significant association between dementia and some or many relational problems experienced by the caregiver. Wolf et al. found in a representative study that almost half of their investigated caregivers provided substantial help with health care activities when assisting an older adult with dementia[33]. They found that caregivers who provided care to patients with both dementia and severe disability were 1.8 times more likely to experience emotional difficulty (95% CI 1.10-2.87).

Caregiver literature has consistently shown that female caregivers are more burdened than male caregivers[34-36]. Males and females experience caregiving differently, and explanations of sex differences in caregiver burden are that males and females live in different structural contexts, which leads to different kinds and intensities of stressors to which people are exposed. In addition, females mostly provide more hours of informal care, experience more negative effects of caregiving and are more sensitive to a feeling of distance between themselves and the person being cared for[35,36]. This might result in a loss of self-esteem, which can ultimately lead to depression[37]. However, in contrast with this theory, we found no difference in the domain of mental problems between male and female informal caregivers. Additionally, and in contrast to Van Dam et al., we found that female informal caregivers stated a significantly lower level of CarerQoL (β -7.8; 95% CI: -13.3 – -2.3) and were 3.00 times more likely to experience relational problems. Surprisingly, we found no significant difference in the intensity of informal care provided by men and women. A possible explanation could be the type of this elderly, predominantly female hip-fracture population for whom caregivers provided informal care in this study. In total 44.7% of the caregivers were male and had to provide a great deal of intense informal care to a loved one with a hip fracture. In addition, almost 25% were male partners with a mean age of 68.8 years (versus 61.2 years for women). This may have led to more equality in the intensity of provided informal care between men and women.

Based on the unadjusted analyses, the intensity of provided informal care was significantly lower for older patients, patients with dementia, patients with a higher GFI and patients already residing in an institution before the fracture. In the

Dutch healthcare system, more frail patients and more patients with dementia reside in nursing homes. They receive more formal care, which could be one of the possible explanations why these patients with a hip fracture require fewer hours of informal care than do elderly patients with a hip fracture residing in the community.

Around half of the patients were discharged to their homes after treatment in the hospital, and subsequent informal care was often imposed on the partner. A common remark during telephone interviews was that they received little or no information in advance about this sudden new 'task' of great intensity, according to our results about the intensity of care provided by partners (β 34.0; 95% CI 20.9 - 47.1).

This study showed that up to 26.0% of the informal caregivers experienced some or many relational problems, 34.1% experienced some or a lot of mental health problems, and 47.5% experienced physical health problems. These problems experienced by those providing informal care can be eased with careful attention from healthcare professionals. Schulz et al. stated that counseling, relaxation training, and respite programs can improve caregiver quality of life by increasing caregiver abilities and confidence to manage daily care challenges[38]. These interventions may delay and reduce the care recipient's institutionalization and reduce re-hospitalization[39,40]. Therefore, we recommend that it is better to inform prospective informal caregivers of patients with a hip fracture about their task at an early stage in the hospital setting. Another important aspect that applies particularly in the case of a patient with a hip fracture is properly educating informal caregivers about the expected course of recovery[17]. Naturally, this varies from patient to patient. The goal of the recovery after a hip fracture is to restore the previous level of ADL. In practice, however, there is a considerable gap between this goal and reality. First, the high mortality of up to 30% in the general population in the first year must not be underestimated[13]. Second, the level of frailty in the aging population is increasing, and there is a delicate balance between the physical, cognitive and social aspects[41]. Our study showed that all participants receiving a total GFI score of 4 and above and were frail. Problems tend to persist in this growing group of elderly with a hip fracture in terms of poorer conditioning with decreased mobility and reduced QoL[14]. Providing realistic expectations for recovery when educating patients and their informal caregivers can help. Nahm et al. reported that informal caregivers often state that their loved one does not get the right kind and amount of care and rehabilitation

in the rehabilitation environment[17]. Given this mismatch, informal caregivers must be better informed about the goal of rehabilitation, which is to assist patients with their recovery, and about the role of informal caregivers, which is to motivate their loved one to do the exercises themselves or assisted by others.

As in any survey, the results are subject to the constraints of sample design, participant response, variables asked, and outcomes used. Because this a cross-sectional survey in which informal caregivers were not followed over time, we are unable to comment on the causal processes that underlie the observed CarerQoL. When interpreting the results of the three groups, heterogeneity of the groups must be considered. The number of contact persons approached by telephone who stated that they no longer needed to provide informal care increased in the 3- and 6-month groups. This finding suggests that the group still receiving informal care at 6 months is an older and frailer group, in which the number of patients with dementia, the number of patients who had been living in an institution before their hip fracture and the GFI score are higher (table 1). Another limitation is that non-response bias cannot be excluded in this study because no demographic data could be collected for contact persons (potential caregivers) who could not be reached by telephone. We could have missed informal caregivers who were too busy or perhaps overburdened so that they were not at home at the time of our call; therefore, our results must be interpreted with caution. However, we randomly selected a subset of individuals, and we discovered no significant difference in patient demographics between responders and non-responders. Response bias could also have had an impact on how caregivers completed the CarerQoL-VAS and the Carer-QoL-VAS 'transfer' because we administered our results by phone and we verbally asked for a score between 0 (completely unhappy) and 10 (completely happy). It could be possible that caregivers provide a socially desirable response that may affect the response in some way[42].

A strength of this study is the use of the CarerQoL-7D instrument to measure the CarerQoL of the informal caregivers. In contrast to the first limitation given above, a cross-sectional study is the primary source of evidence for measuring this construct. The great benefit of the CarerQoL-7D instrument over earlier studies that measured the burden on informal caregivers is the fact that it can measure positive dimensions as well as the burden, such as satisfaction and support received from others. In this study, informal caregivers experienced considerable support and satisfaction, in agreement with informal caregivers in

other populations[31]. In total, 79.5% of caregivers stated that their well-being would remain the same or even decrease if they could give the informal care tasks free of charge to another person chosen by them and the patient, despite the time investment and mental and physical burden of informal care. This is also reflected in the result from the 'satisfaction' and 'support' domains in the CarerQoL-7D. Another strength, in contrast with Van Dam et al., is that we included caregivers from a homogenous group of 123 hip fracture patients. As we mentioned before, an important aspect is to properly educate informal caregivers about the expected course of recovery. This aspect depends on the study population and is more difficult in a heterogeneous geriatric population that includes stroke, elective, trauma and other patients than in our study, which included caregivers of patients with a hip fracture.

To examine in more detail the course of the burden on informal caregivers for patients with a hip fracture, expressed by the intensity of provided informal care and the CarerQoL, it would be valuable to conduct a prospective observational study. An advantage of this study would be that one can follow change over time in particular individuals within a cohort. This would enable us to relate CarerQoL to particular exposures and to further define these exposures with regards to presence, timing and chronicity. This could help healthcare providers to focus more on caregiver CarerQoL, with attention to physical- and mental health problems that informal caregivers frequently report.

Conclusions

Informal caregivers, especially partners, are faced with providing care of greater intensity to elderly patients during the first 6 months after a hip fracture. The CarerQoL was not associated with the intensity of the provided informal care. As the Dutch healthcare system undergoes reform, the pressure on informal caregivers will only increase. This study shows that a considerable group of informal caregivers for elderly patients with a hip fracture experienced relational, physical and mental health problems that stemmed from providing intensive informal care during the first 6 months.

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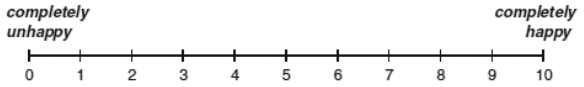
Supplemental file. Care-related Quality of Life instrument

We would like to form an impression of your caregiving situation. Please tick a box to indicate which description best fits your caregiving situation at the moment.

Please tick only one box per description: 'no', 'some' or 'a lot of'.

	no	some	a lot of	
I have	❑	❑	❑	fulfillment from carrying out my care tasks.
I have	❑	❑	❑	relational problems with the care receiver *(e.g., he/she is very demanding or behaves differently; we have communication problems).*
I have	❑	❑	❑	problems with my own mental health *(e.g., stress, fear, gloominess, depression, concern about the future).*
I have	❑	❑	❑	problems combining my care tasks with my own daily activities *(e.g. household activities, work, study, family, leisure activities).*
I have	❑	❑	❑	financial problems because of my care tasks.
I have	❑	❑	❑	support with carrying out my caretasks, when I need it *(e.g., from family, friends, neighbours, acquaintances).*
I have	❑	❑	❑	problems with my own physical health *(e.g., more often sick, tiredness, physical stress).*

How happy do you feel at the moment? Please place a mark on the scale below that indicates how happy you feel at the moment.



CHAPTER 8

Burden of illness of hip fractures in elderly Dutch patients

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ABSTRACT

Introduction: Hip fractures are associated with high mortality, reduced quality of life and increased healthcare utilization, leading to an economic burden to society. The purpose of this study is to determine the burden of illness of hip fractures in elderly Dutch patients for specific time periods after surgery.

Methods: Patients with a hip fracture above the age of 65 were included in the study. In the one-year period after surgery, patients were asked to complete a set of questionnaires pre-injury (retrospectively), and 1 week, 1 month, 3 months, 6 months and 12 months after surgery. The set of questionnaires included the Euroqol 5D (EQ-5D-3L), the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ). Health-related quality of life was calculated using Dutch tariffs. Costs were calculated using the methodology described in the Dutch costing manual.

Results: Approximately 20% of patients with a hip fracture died within one year. Health-related quality of life was significantly reduced compared to pre-injury values and patients did not recover to their pre-injury values within one year. Total costs in the first year after injury were €27,573, of which 10% were due to costs of the procedure (€2,706). Total follow-up costs (€24,876) were predominantly consisting of healthcare costs. Monthly costs decreased over time.

Conclusions: Hip fractures lead to a burden to patients, resulting from mortality and health-related quality of life reductions, and to society, due to (healthcare) costs. The results of this study can be used in future economic evaluations.

Keywords: Hip fractures; Elderly; Burden of illness; Costs; Health-related quality of life

INTRODUCTION

Hip fracture is a severe fracture attributable to bone fragility and predominantly affects an already frail population. A distinction can be made between low-energetic and high-energetic traumas, with low-energetic traumas affecting an older population. The burden of hip fractures on healthcare and society is very high. In 2010, the number of hip fractures in the European Union was over 600,000[1]. Given the aging population, the number of hip fractures is projected to grow in the coming decades[2]. Hip fractures can result in complications, chronic pain, reduced quality of life and premature death[3-5]. Next to the clinical burden to patients, hip fractures lead to medical consumption, including hospitalizations, and associated healthcare costs. In 2010, the estimated economic burden of hip fractures in the European Union due to use of healthcare services was €19 billion[1]. In addition to the burden on the healthcare budget, a patient's social environment is likely to be affected, because of emotional reasons and because of an increased need for informal care[6]. Finally, hip fractures potentially result in productivity losses, particularly due to a patient's inability to perform unpaid work, as the proportion of patients with paid work is generally small due to the population's high age. The prevention and optimal treatment of hip fractures is therefore of crucial importance. The efficiency of prevention and treatment options is, given the economic burden, likely to be an increasingly important factor deciding on the care pathway. For this purpose, data on both cost and effects are required to inform health economic models. One of the benefits of using models for economic evaluations is their ability to extrapolate outcomes beyond the observed period. For this purpose, it is crucial that the pattern of costs and health-related quality of life (HRQOL) over time is identified, because costs and HRQOL can be different directly after surgery than after a period of time.

Previous publications on per patient healthcare costs of hip fractures in the Netherlands have reported cost estimates between €19,741 and €26,355 (inflation corrected to 2018 values)[7-10]. Next to costs, information on HRQOL is crucial for health economic studies. HRQOL is generally presented in a utility value, which scores HRQOL on a scale from 0 (death) to 1 (perfect health). The impact of hip fractures on HRQOL has previously been assessed in the Netherlands in other studies. A study in the period 2001-2002 showed that utility scores for patients with hip fractures was severely reduced compared to the average Dutch population: 2.5 months after injury the average utility was 0.43 and 0.67 after 24

months[11]. More recent Dutch studies did not report utility values, but have been reported in international studies. A recent systematic review showed that HRQOL deteriorates in the first period after a hip fracture, after which patients recover to a level below their pre-injury level[5]. The primary objective of the current study is to provide a comprehensive overview of the burden of illness of hip fractures in an elderly population in the Netherlands. For this purpose, we examine, over a period of one year after hip fracture, life expectancy, HRQOL, and healthcare and productivity costs in a sample of Dutch elderly patients with a hip fracture who underwent surgery. A distinction in monthly costs and utilities over time will be examined, so that these estimated can be used in model-based economic evaluations.

METHODS

Dataset

The study used the Brabant Injury Outcome Surveillance (BIOS) database, a multicentre observational follow-up cohort study, which is described elsewhere[12]. Data were collected in the period August 2015-November 2016. For the current study, the subset of hip fracture patients was selected. The dataset contained 821 patients with hip fracture over the age of 65 with a hip fracture that underwent surgery. Patients were followed for 1 year, with measurements pre-injury (T0; measured retrospectively), and 1 week (T1), 1 month (T2), 3 months (T3), 6 months (T4) and 12 months (T5) after injury. The dataset contained information on survival, HRQOL, frailty and healthcare costs and productivity costs. Only patients who participated in the prospective study were included in the sample. Patients that died during hospitalization (n=2) were excluded from the study, since they were unable to provide informed consent after surgery. Furthermore, three patients with pathological fractures were excluded. No patients were excluded because of language barrier, although language barrier was an exclusion criterion. Ethical approval was received from the Medical Ethics Committee Brabant, the Netherlands (NL50258.028.14). Informed consent was obtained from all individual participants included in the study.

Measurement and valuation of health-related quality of life

HRQOL was expressed in utilities, derived from the EQ-5D-3L. This generic instrument is used to measure health status using five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each dimension having three levels[13]. Health status descriptions from the EQ-5D

can be valued using tariffs from preference elicitation studies to calculate utilities, which can be used in economic evaluations. Utility scores were derived from the EQ-5D using the Dutch value set[14]. Negative values were also possible and represent health states worse than death. Utility values calculated with the Dutch value set range from -0.329-1.000.

Measurement and valuation of costs

Costs of the surgical procedure were estimated using a micro-costing study. For this purpose, the time duration of all hip surgery procedures in 2017 in level 1 trauma centre Elisabeth-Tweesteden Ziekenhuis (ETZ; Tilburg, the Netherlands) was used. The costs associated with using the operation room (per minute, including overhead costs) and costs of prostheses was based on information from the financial department of ETZ. Involvement of medical personnel was based on expert opinion, and valued using the Dutch costing manual[15].

Medical consumption was measured with the iMTA Medical Consumption Questionnaire (iMCQ)[16]. The questionnaire included questions on utilization of home care, general practitioner, rehabilitation, long-term care, psychologist and paramedical care. Except for the initial hospitalization resultant of the hip fracture and one outpatient visit following surgery (based on expert opinion), hospital costs were not included in the database. Dutch health economic guidelines require studies to be carried out from a societal perspective, meaning that all costs and effects should be included in the analyses[17]. Therefore, not only healthcare costs were included in the study. The iMTA Productivity Costs Questionnaire (iPCQ) was used to measure productivity costs[16,18]. Data on unpaid work (e.g. household activities) were not collected. Healthcare consumption and productivity losses were valued using the most recent update of the Dutch costing manual[15]. The friction cost method was used to establish productivity costs. Prices were indexed to 2018 price level. Data on informal care and associated costs were not available.

Missing data

To make optimal use of available data, missing data were imputed. For this purpose, HRQOL was imputed using multiple imputation by chained equations[19] and linear intrapolation. Costs were imputed using multiple imputation and mean imputation for individual items. Full details about the imputation procedures are provided in the supplemental file.

Statistical analyses

Utility values were presented for patients alive at each specific time point. In addition to utility values, QALYs were calculated by combining survival and quality of life. Since the follow-up of the current study was one year, and utilities are maximized at 1.00, the maximum QALY value in this study was 1.00. Costs were presented as total annual costs and average monthly costs for specific time periods. Total annual costs include costs estimates for patients that died during the study period.

Subgroup analyses were performed with respect to one year survival (whether patients survived the first year after injury or not), gender, age (age groups 65-69, 70-79, 80-89, and ≥90), comorbidity, pre-injury living situation and frailty. Statistical analyses were performed using Stata 15.1 (Statacorp).

RESULTS

The average age in the patient population was 80 years (SD 8.63; range 65 – 101). The majority of patients were female. More than 80% of patients had one or more comorbidities at moment of injury. Most common comorbidities were heart malfunctions (29% of patients), arthrosis (28%), dementia (23%) and osteoporosis (18%). Pre-injury HRQOL was 0.72 (SD 0.28; range -0.204 – 1.00). Half of the patients were identified as frail on the Groningen Frailty Indicator (GFI). A total of 21% of patients lived in an institution pre-injury.

Table 1. Patient characteristics

Variable	Mean	Std. err.
Age	80.2	0.349
Gender (% female)	70.3%	0.018
One or more comorbidities pre injury	82.5%	0.015
Health-related quality of life pre injury	0.722	0.011
Frail elderly (GFI ≥ 4) pre injury	52.1%	0.021
Living in an institution pre injury	21.2%	0.016

GFI: Groningen Frailty Indicator[20]

Survival and health-related quality of life

Survival data were available for 820 patients. The survival rate in the first 30 days after injury was 99.5% [95% CI: 98.7-99.8]. One-year survival was 83.3% [95% CI: 80.3-86.0]. Mortality of 80 year olds in the Dutch population is 4.3%[20].

Pre-injury HRQOL data were available for 625 patients. Pre-injury HRQOL for this patient population was on average 0.72. This is approximately 13% lower than the Dutch population norm utility value of 0.83 of people over the age of 75[21]. Figure 1 shows the development of utility values in the first year after injury. Hip fractures resulted in a sharp decrease in HRQOL compared to patients' pre-injury utility value. With time, patients gradually recovered from the hip fracture, but their utility value after one year was still substantially lower than their pre-injury utility. The average QALY value for patients in the year during follow-up was 0.528 (95% CI: 0.504-0.553).

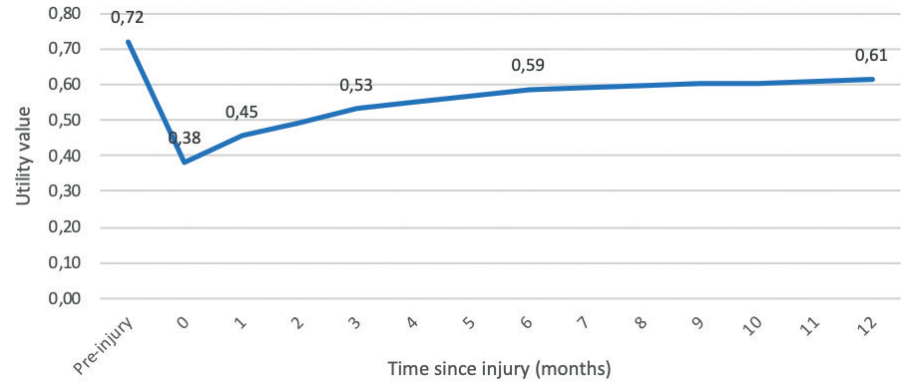

Figure 1. Utility values for patients with hip fracture over time

Costs

Table 2 shows that total costs following the first year after a hip fracture were €27,573. Costs of the surgical procedure was €2,706 (range €1,734 – €4,397), accounting for 10% of total costs. Data on costs in the period following surgery were available for 663 patients in the BIOS study. Table 2 shows that average total healthcare costs in the year following injury were €24,760 (range €21,113 – €28,406), accounting for 90% of total costs. Productivity costs were minor in the year following a hip fracture, due to the high age of the population. The first month after injury was the most costly; healthcare costs accumulated to €6,932. The majority of costs in the first month was related to hospitalizations (>50% of total monthly costs). The average length of stay in the hospital following the fracture was 8.6 days (median 7; range 1 – 63). The second largest cost component was long-term care stay (>40%). Almost 54% of patients returned home after hospital discharge. As time progresses, average monthly costs decreased; from over

€3,193 in months 2 and 3 after injury to €1,206 in months 7 to 12 after injury. In months 7 to 12 after injury, the vast majority of monthly costs (>80%) was due to long-term care stay.

Subgroup analyses

Table 3 presents the results of the subgroup analyses. Although follow-up costs for patients who died within the study period were higher than for patients who survived the first year after injury, the confidence intervals around these estimates were overlapping. Male patients incurred significantly more QALYs than female patients. Younger patients on average had lower follow-up costs and more QALYs than older patients. Costs for patients with comorbidities were higher and health effects than for patients without comorbidities. Confidence intervals of costs for patients living at home pre-injury and institutionalized patients overlapped. QALYs were significantly higher for patients living at home pre-injury. Costs for frail elderly patients were higher than for non-frail patients. QALYs were significantly higher for non-frail patients.

Table 2. Average costs (in euros)

	Total costs			**Monthly follow-up costs**							
	Total costs	Procedure costs (n=321)	Annual follow-up costs (n=663) *	Month 1 (n=663) *		Months 2-3 (n=652)		Months 4-6 (n=621)		Months 7-12 (n=598)	
	Mean	Mean	Mean	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Medical costs	27,466	2,706	24,760	6,932	1,005-18,134	3,193	0-26,645	1,770	0-20,489	1,205	0-15,770
Productivity costs	107	N/a	107	61	0-10,125	16	0-2,394	2	0-1,551	1	0-849
Total	27,573	2,706	24,867	6,993	1,005-18,134	3,209	0-26,645	1,773	0-20,489	1,206	0-15,770

* Excluding procedure costs

Table 3. Subgroup analyses

	Number	**Total annual follow-up costs ***		**QALYs**	
		Mean	95% CI	Mean	95% CI
All patients	625	€25,395	€21,569-€29,221	0.528	0.504-0.553
Deceased					
- Alive after 12 months	516	€23,909	€19,887-€27,931	0.601	0.578-0.624
- Not alive after 12 months	109	€32,431	€22,462-€42,401	0.185	0.138-0.231
Gender					
- Male	187	€19,967	€13,960-€25,975	0.588	0.546-0.630
- Female	438	€27,712	€22,845-€32,580	0.503	0.473-0.532

Table 3. Continued.

	Number	Total annual follow-up costs *		QALYs	
		Mean	95% CI	Mean	95% CI
Age at injury					
- 65-69	101	€9,911	€3,423-€16,399	0.714	0.673-0.754
- 70-79	177	€14,822	€9,341-€20,303	0.634	0.591-0.676
- 80-89	246	€32,651	€26,203-€39,100	0.457	0.419-0.494
- ≥90	101	€41,733	€28,756-€54,711	0.333	0.277-0.388
Comorbidity					
- No comorbidities	108	€16,371	€10,337-€22,405	0.731	0.689-0.772
- One comorbidity or more	511	€27,418	€22,882-€34,954	0.485	0.459-0.512
Pre-injury living situation					
Home	486	€26,778	€22,198-€31,357	0.600	0.576-0.625
Institutionalized	132	€20,709	€12,562-€28,856	0.264	0.220-0.308
Frailty pre-injury					
Non-frail (GFI<4)	296	€16,044	€11,837-€20,250	0.725	0.701-0.749
Frail (GFI≥4)	329	€33,942	€27,623-€40,260	0.348	0.318-0.379

* Excluding procedure costs

DISCUSSION

This study assessed the burden of illness of hip fractures. Approximately 20% of patients died within one year. Patients experienced reduced HRQOL and did not recover to their pre-injury HRQOL level within one year. Average annual healthcare costs were €27,573, of which 10% was related to the surgical procedure and 90% was due to follow-up costs in the first year after injury. Follow-up costs were found to be concentrated in the first period after injury.

Comparison to other studies

The findings on the pattern of HRQOL after a hip fracture in the current study concur with earlier findings in a recent literature review, in that HRQOL is severely reduced after a hip fracture and patients recover to a level below their pre-injury HRQOL[5]. With respect to costs, other studies also found that incremental costs declined over time since injury[8, 22-24]. Comparing international cost estimates is complicated due to international differences in, among others, unit cost prices, inclusion of cost categories, finance systems, healthcare pathways and patient populations.

Over the years, various studies assessed per patient costs of hip fractures in the Netherlands. In 1999, per patient were estimated to be €13,600 (inflation corrected to 2018: €19,741)[7]. A study that collected data between 2003 and 2007, estimated healthcare costs of €18,233 (2018: €21,975)[8]. Another study, with data collected between 2008 and 2011 estimated healthcare costs for the first year to be 23,869 (2018: €26,355)[9]. Using 2012 data, per patient healthcare costs were estimated to be €19,717 (2018: €21,770), with additional costs due to lost productivity of €34,518 (2018: €38,113)[10]. When comparing the results of the current study to previous Dutch studies, the current estimates of healthcare costs resemble findings in three of these earlier studies[8-10]. The study by Meerding et al. estimated lower healthcare costs (€13,600; 2018 values €19,741) for a period of 9 months after injury[7]. Costs were lower than in the current study for multiple reasons: the follow-up period was shorter than in the current study; institutionalized patients were excluded; and lower unit cost prices were used. Productivity costs were previously estimated in one Dutch study[10], and were much higher than estimated in the current study, which was likely to be explained by the high age of the patient population; only elderly patients were included in the current study. As such, the majority of patients was already retired and did not incur productivity costs from paid work.

Limitations

Cost estimates of the surgical procedure were based on information from one hospital only, supplemented with expert opinion. This hospital is a level 1 trauma centre (i.e. the highest level in the Netherlands), which might not be representative for all hospitals in the Netherlands. Ideally, multiple hospitals with varying levels of trauma care would have been included and expert input would have been replaced by observed parameter input on involvement of medical personnel. Furthermore, procedure costs were not determined for the same patients who were included in the follow-up cost study in BIOS. Combining the data into a single cost estimate therefore assumes that the procedure costs can be generalized to the patients in the BIOS study.

Besides hospital costs related to the surgical procedure and an assumed one-time follow-up outpatient visit, hospital-related resource use was not measured in the BIOS study. Follow-up hospitalizations due to complications were not included in the study either. This has resulted in an underestimation of total costs. In addition, the dataset did not contain information on informal care use. As such, costs related to informal care could not be taken into account. An earlier study in informal caregivers in a subsample of this patient population showed that the use of informal care is substantial: the vast majority of patients had received informal care (only 11% of contact persons had never provided informal care); in the first month after injury patients on average received 50 hours of informal care per week and after six months patients received 25 hours of informal care per week[6]. Such volumes of care are associated with a monthly cost of €2,740 and €1,370 respectively. Considering the size of total monthly costs calculated in this study (€6,933 and €1,929 in months 1 and 6, respectively), the absence of informal care costs is therefore an important hiatus of the study. Finally, no data were collected on productivity costs from unpaid work. Because the majority of patients is already retired in this patient population, productivity costs from paid work are limited. Performing unpaid work is less age dependent, e.g. a patient aged 90 might still be able to perform household activities. Therefore, hip fractures potentially lead to productivity losses and associated costs from unpaid work in this patient population. Future research could focus on this type of productivity losses.

Data were only collected from patients who were willing to participate in the BIOS study. Patients that died during the initial hospitalization after the hip fracture were therefore not included in the sample. Likewise, patients with a very bad prognosis might have opted not to participate in the study as well. This selection bias might have

led to an underestimation of the burden of illness. This is apparent from the 30-day survival rate in BIOS (99.5%), which is much lower than the mortality in the total hip fracture populations with a 30-day survival rate of 86.7% reported in a systematic literature review[26].

Pre-injury HRQOL was determined retrospectively. This may have caused recall bias. Prospective data collection is not possible for pre-fracture patients. A recent systematic literature review showed that use of retrospective assessment of pre-injury quality of life is the most common method to collect quality of life before injury; this method was used 29 in of 31 identified studies[27]. The use of population values has been suggested as an alternative. However, these might not be an adequate reflection of people with high risk of hip fractures, as these high-risk people might already have more health problems and worse HRQOL compared to matched controls in the overall population, as was indicated by the 13% lower utility values pre-injury found in this study.

Implications

The results of this burden of illness study can be used in future economic evaluations in elderly patients with hip fractures. In particular, the distinction of utility values and monthly costs at different points in time after surgery can prove useful for health economic modelling, especially when costs and effects are extrapolated beyond the follow-up period of the study.

The objective of this study was to estimate the burden of illness in elderly Dutch patients. Hence, we adhered to Dutch guidelines with respect to quantifying utilities and costs. The use of utility tariffs for other countries might result in different utility values, but the pattern of HRQOL over time after injury is unlikely to be different in other countries. This study used the friction cost method to monetarize productivity losses from paid work. Alternatively, the human capital method could have been used. However, the results would be similar, since the majority of patients in the sample was over the retirement age.

Conclusions

Patients with hip fractures experience a significant burden in the period after injury, as they experience an increased mortality risk and reduced HRQOL. In addition, hip fractures lead to a substantial economic burden, particularly due to costs of healthcare consumption. The results of this study can be used in future cost-effectiveness studies.

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SUPPLEMENTAL FILE

Missing data

Health-related quality of life

To ensure the optimal use of available data, missing data were imputed in a multi-step process. Firstly, individual missing dimensions of the EQ-5D were imputed using multiple imputation, using chained equations to enable imputation of missing values in multiple variables [1]. The non-missing dimensions of the EQ-5D and VAS at the same time point, plus gender and age at injury were used as independent variables. Secondly, if T2 EQ-5D questionnaires were missing in its entirety, the EQ-5D dimensions at T2 were imputed using multiple imputation, using all five EQ-5D dimensions at T1, the same EQ-5D dimension at later time points, gender and age at injury as independent variables. Thirdly, when EQ-5D data were missing in its entirety at a particular measurement other than T2, linear intrapolation between time points of utility values was applied. Linear intrapolation was only applied for time points after surgery. When utility scores at T5 were missing, these were assumed equal to utility scores at T4. Finally, EQ-5D utilities were imputed using multiple imputation, using all available EQ-5D utilities at other time points as independent variables. Table A1 shows the percentages of missing items that were imputed at each step of the imputation procedures.

Imputation of EQ-5D dimensions (step 1 and 2) were performed using ordered logit regression models, because EQ-5D dimensions are categorical variables. For imputations of utility values (step 4) predictive mean matching was used [2]. Predictive mean matching provides a linear prediction and imputes missing values by nearest-neighbour donor, with the distance based on the predicted value of the missing variable from the linear regression. Using predictive mean matching ensures that the distributions of utility values (bound between -0.329 and 1.000 in the Dutch value set) are preserved.

Table A1. Details imputation procedure EQ-5D dimensions and utilities

Imputed variable	Complete items	Missing items	Total items	% missing
Step 1. Imputing single EQ-5D Dimensions using multiple imputation				
T0 EQ-5D Mobility	651	5	656	0.8%
T0 EQ-5D Self care	652	4	656	0.6%
T0 EQ-5D Usual activities	650	6	656	0.9%
T0 EQ-5D Pain / Discomfort	644	12	656	1.8%
T0 EQ-5D Anxiety / Depression	652	4	656	0.6%
T1 EQ-5D Mobility	232	7	239	2.9%
T1 EQ-5D Self care	239	0	239	0.0%
T1 EQ-5D Usual activities	238	1	239	0.4%
T1 EQ-5D Pain / Discomfort	239	0	239	0.0%
T1 EQ-5D Anxiety / Depression	238	1	239	0.4%
T2 EQ-5D Mobility	591	10	601	1.7%
T2 EQ-5D Self care	597	4	601	0.7%
T2 EQ-5D Usual activities	595	6	601	1.0%
T2 EQ-5D Pain / Discomfort	595	6	601	1.0%
T2 EQ-5D Anxiety / Depression	597	4	601	0.7%
T3 EQ-5D Mobility	618	4	622	0.6%
T3 EQ-5D Self care	620	2	622	0.3%
T3 EQ-5D Usual activities	616	6	622	1.0%
T3 EQ-5D Pain / Discomfort	617	5	622	0.8%
T3 EQ-5D Anxiety / Depression	618	4	622	0.6%
T4 EQ-5D Mobility	551	7	558	1.3%
T4 EQ-5D Self care	558	0	558	0.0%
T4 EQ-5D Usual activities	557	1	558	0.2%
T4 EQ-5D Pain / Discomfort	550	8	558	1.4%
T4 EQ-5D Anxiety / Depression	557	1	558	0.2%
T5 EQ-5D Mobility	540	4	544	0.7%
T5 EQ-5D Self care	544	0	544	0.0%
T5 EQ-5D Usual activities	542	2	544	0.4%
T5 EQ-5D Pain / Discomfort	537	7	544	1.3%
T5 EQ-5D Anxiety / Depression	540	4	544	0.7%
Step 2. Imputing single T2 EQ-5D dimensions using multiple imputation				
T2 EQ-5D Mobility	591	17	608	2.8%
T2 EQ-5D Self care	597	16	613	2.6%
T2 EQ-5D Usual activities	595	17	612	2.8%
T2 EQ-5D Pain / Discomfort	595	16	611	2.6%
T2 EQ-5D Anxiety / Depression	597	16	613	2.6%
Step 3. Imputing utility values using linear intrapolation				

Table A1. Continued.

Imputed variable	Complete items	Missing items	Total items	% missing
T2 Utility value	9,170	416	9,586*	4.3%
T3 Utility value	8,783	1148	9,931*	11.6%
T4 Utility value	7,761	1150	8,911*	12.9%
T5 Utility value	8,423	264	8,687*	3.0%
Step 4. Imputing utility values using multiple imputation				
T1 Utility value	230	411	641	64.1%
T2 Utility value	621	52	673	7.7%
T3 Utility value	674	112	786	14.2%
T4 Utility value	656	121	777	15.6%
T5 Utility value	695	95	790	12.0%

* Imputed dataset

Costs

Missing resource items in completed iMCQ questionnaires were imputed using the mean value for each individual item. Multiple imputation was not deemed appropriate for resource use items due to volatility and unpredictability of resource use. If iMCQ questionnaires were missing in its entirety at a particular measurement, total costs were imputed using multiple imputation, using age at injury, health-related quality of life and costs at all available time points as independent variables. Before the multiple imputation procedure, costs were log-transformed to account for non-normality in the data. Table A2 shows the percentages of missing items of costs that were imputed in the imputation procedure.

Table A2. Details imputation procedure healthcare costs

Imputed variable	Missing items	Total	% missing
T2 Total healthcare costs	125	671	18.6%
T3 Total healthcare costs	218	793	27.5%
T4 Total healthcare costs	284	748	38.0%
T5 Total healthcare costs	318	750	42.4%

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CHAPTER 9

Summary

A hip fracture is a serious event in the aging population. With the rising life expectancy across the globe, it seems reasonable that hip fractures will increase a burden to both individual and society. The overall aim of this thesis was to evaluate outcome in patients with a hip fracture, concerning 3 parts: medical decision-making **(part I)**, Quality of Life **(part II**) and societal impact **(part III)**.

PART I MEDICAL DECISION-MAKING

Part I provided information to aid healthcare providers, patients and relatives in medical decision-making for surgical repair or palliative care. This part contained three research questions:

- What are the differences in mortality, Quality of Life (QoL), functional outcome and costs between nonoperative (NOM) and operative management (OM) of hip fractures in patients above 65 years? **(chapter 2)**
- Which are the best predictor variables for 30-day and for 1-year mortality in patients above 65 years with a hip fracture? **(chapter 3)**
- Which factors influencing the decision-making of treatment for hip fractures in frail patients? **(chapter 4)**

This part focused on risk profiles and factors for poor outcome in patients after hip fracture to support clinicians, patients and relatives in tailoring treatment for medical decision-making. **Chapter 2** presented a systematic review and meta-analysis to provide an overview of studies comparing operative management (OM) with nonoperative management (NOM) with differences mortality, health-related QoL [(HR)QoL], functional outcome, and costs in in patients above 65 years. In general, 30-day and 1-year mortality were higher in the non-operatively treated group. None of the included studies compared outcome measures of (HR)QoL, functional outcome or healthcare costs between OM and NOM. The unadjusted pooled 30-day and 1-year mortality odds ratios (OR) were almost 4 times higher for NOM compared to OM. This systematic review demonstrated that only a few observational studies with small number of patients comparing NOM with OM have been published.

In **chapter 3** we developed and internally validated the Brabant Hip Fracture Score (BHFS). We developed two easy to use clinical prediction models for 30-day (BHFS-30) and 1-year (BHFS-365) mortality in a cohort study of 916 operatively treated patients of 65 years and older with a hip fracture. Independent

predictors of 30-day mortality were: age, gender, living in an institution, Hemoglobin (Hb), respiratory disease, diabetes and malignancy. In addition, cognitive frailty and renal insufficiency, were selected in the BHFS-365. Both models showed acceptable discrimination after internal validation (area under the receiver operating characteristic curve: 0.71 & 0.75 respectively) and no lack of fit (Hosmer-Lemeshow goodness-of-fit test: $p>0.05$). In clinical practice a cutoff of BHFS-30 ≥24 could identify frail older patients at high risk for early mortality and could support clinicians, patients and families in tailoring treatment for medical decision-making.

In **chapter 4** we used a seven-stage concept mapping method to identify factors that could influence the decision to recommend OM or NOM in frail older patients with a hip fracture. The factors were operationalized into a decision-support tool to identify patients potentially eligible to discuss NOM by using data from the Brabant Injury Outcome Surveillance (BIOS), a multicenter prospective observational follow-up cohort study. The decision-support tool consisted of four items: (1) pre-fracture health status (HS); (2) living in an institution; (3) frailty score; and (4) two or more comorbidities. The total score was calculated by summing the scores of the four items. A summing cut-off score of ≥3 represent an optimal cut-off for patients potentially eligible to discuss NOM.

PART II QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS

This part described prognostic factors of QoL and psychological distress in patients after hip fracture with two research questions:

- What is the effect of frailty on QoL in patients after hip fracture? **(chapter 5)**
- What is the prevalence and what are prognostic factors of psychological distress in patients with a hip fracture? **(chapter 6)**

In **chapter 5** we examined the effect of frailty on HS and QoL in patients after hip fracture. From the BIOS study we included 696 patients with a hip fracture aged 65 years and older or proxy respondents for patients with cognitive impairment. In total, 371 patients (53.3%) were considered frail. Frailty was negatively associated with HS (β -0.333; 95% Confidence interval (CI) -0.366 to -0.299), self-rated health (β -21.9; 95% CI -24.2 to -19.6), and capability wellbeing (β -0.296; 95% CI -0.322 to -0.270) in patients 1 year after hip fracture. After adjusting for confounders, including death, prefracture HS, age, prefracture residential

status, prefracture mobility, ASA and dementia, associations were weakened but remained significant. We revealed that frailty is negatively associated with QoL 1 year after hip fracture, even after adjusting for confounders.

In **chapter 6** we determined the prevalence and prognostic factors for psychological distress after a hip fracture. From the BIOS population we included 570 patients and the prevalence of psychological distress ranged from 36% at 1 week to 31% at 1 year after hip fracture. Frailty at onset of hip fracture was the most important prognostic factor of symptoms of depression (OR, 2.74; 95% CI 1.41 to 5.34) and anxiety (OR, 2.60; 95% CI 1.15 to 5.85) on average in the year following hip fracture. Frailty was no prognostic factor of symptoms of posttraumatic stress (PTS; OR, 1.97; 95% CI 0.42 to 9.23).

These findings suggested that early identification of prefracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment, with respect to QoL and psychological distress.

PART III SOCIETAL IMPACT

This part focused on societal impact of hip fractures with respect to informal care and the burden of illness. Two research questions were investigated:

- What is the impact for informal caregivers of providing informal care to patients after hip fracture? **(chapter 7)**
- What is the burden of illness of hip fractures in the Netherlands? **(chapter 8)**

In **chapter 7** we determined the nature, intensity and the care-related Quality of Life (CarerQoL) of informal caregivers of hip-fractured patients in the first 6 months. In this cross-sectional study with hip fracture cohort data from the BIOS study the primary informal caregivers of patients with a hip fracture were interviewed about the informal care provided after 1, 3 or 6 months following hip fracture. In total, 123 primary informal caregivers were included. The CarerQoL-7D score was on average 83.7 (SD 15.0) after 1, 3 and 6 months, and there were no major differences between the measurement time points. The average amount of informal care per patient was 39.5 hours per week during the first 6 months. Partners of patients with a hip fracture provided significantly more hours of informal care (β 34.0; 95% CI: 20.9 to 47.1). Female informal caregivers stated a significantly lower level of CarerQoL (β -7.8; 95% CI: -13.3 to -2.3). Female

caregivers were 3-times more likely to experience relational problems (adjusted OR (aOR) 3.02; 95% CI 1.08 to 8.43). Caregivers provided care at 6 months were associated with physical health problems (aOR 2.54; 95% CI 1.05 to 6.14). A considerable group of informal caregivers experienced relational, physical and mental health problems that stemmed from providing intensive informal care during the first 6 months.

In **chapter 8** we determined the burden of illness of hip fractures in older Dutch patients for specific time periods after surgery. From the BIOS study we included patients of 65 years and older with a hip fracture and used the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ). HS was significantly reduced compared to pre-injury values and patients did not recover to their pre-injury values within 1 year. The average Quality-Adjusted Life Year (QALY) value for patients in the year during follow-up was 0.528 (95% CI: 0.504 to 0.553). The average annual healthcare costs were €27,573 per patient. QALYs were significantly higher for non-frail patients (mean 0.725; 95% CI: 0.701-0.749 vs. 0.348; 95% CI: 0.318-0.379). QALYs for institutionalized patients were very low with 0.264 (95% CI: 0.220 to 0.308). Costs for frail patients (mean €33,942; 95% CI: €27,623-€40,260) were higher than for non-frail patients (mean €16,044; 95% CI: €11,837-20,250).

These studies showed that hip fractures lead to a burden to patients, resulting from mortality and (HR)QoL reductions, and to society, considering informal caregivers and (healthcare) costs.

CHAPTER 10

General discussion

The overall aim of this thesis was to evaluate outcome in patients with a hip fracture. This chapter addresses methodological considerations, clinical implications and future perspectives in the light of the current literature to improve the clinical management of hip fractures in older patients.

PART I MEDICAL DECISION-MAKING

We demonstrated that only a few observational studies with small number of hip-fractured patients comparing nonoperative management (NOM) with operative management (OM) have been published **(chapter 2)**. No data was found about health-related Quality of Life [(HR)QoL] between those two groups. In operatively treated patients it has been shown previously that health status (HS) is seriously affected by a hip fracture in the physical, psychological, and social domain[1]. The prefracture physical and psychosocial functioning, comorbidity, female gender, nutritional status, type of fracture, postoperative pain, length of hospital stay, and complications seem associated with worse outcome. As a result of associated high mortality, NOM has largely been abandoned, as the benefits concerning mortality of prompt surgical repair have become clear. Nevertheless, the decision to undergo OM versus NOM is less straightforward in patients with pre-existent poor QoL and advanced comorbidities, including cognitive and functional disability[2]. Moreover, QoL in older patients with a hip fracture has been largely ignored. Especially in frail patients with poor QoL, early integration of palliative care is considered appropriate with particular focus on goals of care discussions, pain and symptom management, care planning and coordination, and end-of-life care[3,4]. So far there is a lack of studies addressing this topic, because it was difficult in practice to conceive circumstances in which a trial would be considered ethically. Moreover international literature mainly focus on mortality instead of QoL. In this part of the thesis we tried to overcome this ethical issues to determine in which category of patients NOM could be discussed.

Clinical prediction models contribute to evidence-based input for medical decision-making and provide insight into the relative effects for predictors of mortality. We developed and internally validated the Brabant Hip Fracture Score (BHFS) for 30-day and 1-year mortality in surgically treated older patients **(chapter 3).** These models showed acceptable discrimination and adequate calibration, but external longitudinal validation is needed to evaluate the robustness of the performance of the BHFS. External validation may temper overoptimistic expectations of prediction model performance in independent

data and support general applicability[5]. In addition, implementation of a clinical prediction model is challenging. Most commonly reported barriers to use clinical prediction models were lack of time, irrelevance to some patients, and poor integration with electronic health records[6]. Though awareness of our found predictor variables, including age, gender, living in an institution, Hb, respiratory disease, diabetes, malignancy, cognitive frailty and renal insufficiency, and web-based application can enhance implementation in clinical practice.

Furthermore, we developed an easy to use decision-support tool to identify patients potentially eligible to discuss NOM **(chapter 4)**. We gave insight into which considerations play a role in the medical decision-making for OM or NOM in frail patients in the Netherlands. Current guidelines have no strict advice for frail patients with a hip fracture, as a result of lack of evidence on palliative care in these patients[4,7,8]. Dutch guidelines propagate OM in patients with a life expectancy beyond 6 weeks. Moreover, in the National Institute for Health and Care Excellence (NICE) guidelines NOM is mentioned briefly, with the assumption that surgery should be done and as fast as possible. However, the 'Choosing wisely campaign'[9], 'Niet alles wat kan, hoeft'[10], and 'Zinnige Zorg'[11] have stimulated shared decision-making for patients at high risk for death or severely impaired functional recovery and suggest patients and their families should offered the alternative of care focused entirely on comfort and QoL. Hip fracture in frail patients is an important opportunity to reassess patients' personal healthcare priorities[12] (Figure 1). However, these goal of care discussions should take place earlier in older adults at high risk for falls and traumatic fracture, known as advance care planning[13]. Advance care planning has been shown to improve patient outcomes and satisfaction, and reduced the incidence of anxiety, depression and post-traumatic stress in surviving relatives[14].

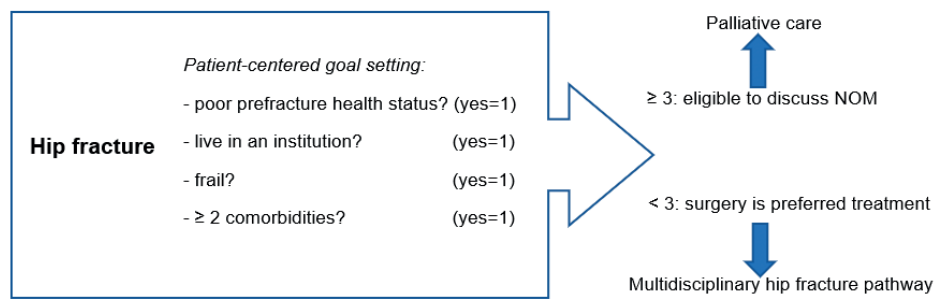

Figure 1. Medical decision-making in patients with a hip fracture
Abbreviations: NOM: nonoperative management; QoL: Quality of Life

Advance care planning could result in a directive of no treatment or no future hospitalization. However, in current practice those directives are rarely seen and individuals fail to complete an advance directive. They seldom discuss their medical treatment preferences, often leaving clinicians with little indication for how they want to be treated[15]. The decision-support tool provides information for the discussion to aid providers in medical decision-making for OM or NOM in frail patients with a hip fracture.

Future perspectives

Future studies should evaluate the quality of prediction of our decision-support tool. The decision-support tool should be validated by being applied prospectively to another cohort of patients, to determine how it would affect their care and what the implications are on the quality of dying and death after decision-making. Also testing for external validity of our decision-support tool is a necessity in order to judge its applicability in general. Future studies should test its suitability in similar groups of patients but in different healthcare systems to extend its cross-national robustness. Preconditions should be a high standard of palliative care and the ability from healthcare providers and relatives that both treatment options are open to discussion. This could be challenging in the implementation of the decision-support tool.

Evidence based guidelines on determination of OM or NOM in frail patients with a hip fracture are lacking. To contribute knowledge on this emerging area of importance, future research should focus on determining the effect of NOM versus OM of hip fractures in a selected group of frail institutionalized elderly on the QoL, level of pain, rate of complications, time to death, satisfaction of the patient (or proxy) and the caregiver with the management strategy. The two-arm non-randomized (observational) multicenter FRAIL-HIP study will contribute widely to the current knowledge about the process of NOM, and may also help updating (international) treatment guidelines on hip fractures[16]. Inclusion criteria for this study are frail institutionalized patients above 70 years with a hip fracture and with a body mass index <18.5, or a Functional Ambulation Category of 2 or lower prefracture, or an American Society of Anesthesiologists (ASA) score of 4 or 5. Treatment decision between OM and NOM will be reached with shared decision-making with patients, families and all relevant healthcare providers. Data will be recorded at 7, 14, and 30 days and at 3 and 6 months after hip fracture. The results of this study will provide insight into the value of NOM in frail hip-fractured patients with a limited life expectancy.

PART II QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS

In the last decades considerable effort has been made to improve care for hip fracture patients. A lot of national and international research is conducted and several dissertations have appeared, concerning fixation techniques[17-19], determinants of outcome[19,20] and economic aspects[17,21].

Orthogeriatric care models and clinical pathways[22,23] were introduced with country standards of care for hip fracture patients in combination with Hip Fracture Audits and Databases[24,25]. Despite these efforts, morbidity and mortality outcome after hip fracture remained essentially unchanged over the last decades[26,27]. Currently, these factors play a major role in evaluating the outcome of a hip fracture. However, QoL deserves more attention, as this may be a more appropriate indicator for the outcome from the patient's perspective. Age younger than 80 years, ASA classification I or II, higher prefracture level of mobility, intracapsular fracture and treatment with osteosynthesis (compare to arthroplasty) were already associated with greater decline in physical HRQoL[28]. A systematic review from Peeters et al. showed already that prefracture physical and psychosocial functioning, comorbidity, female gender, nutritional status, type of fracture, postoperative pain, length of hospital stay, and complications are associated with worse HS and HRQoL[1]. However, QoL that consists of the expectations of an individual for well-being, in hip fracture patients was unknown.

We revealed that a high percentage of individuals do not return to prefracture HS levels within a year on all domains of the EQ-5D. Moreover, we showed that frailty is negatively associated with QoL, adjusted for confounders including death, prefracture EQ-5D utility score, age, prefracture residential status, prefracture mobility, ASA and dementia **(chapter 5)**. We also revealed that frailty at onset of hip fracture was the most important prognostic factor of symptoms of depression and anxiety on average in the year following hip fracture **(chapter 6)**.

Methodological considerations

In our BIOS study we found no significant differences in patients' age and sex between responders and non-responders. However, several statistical bias types cannot be ruled out.

First, selection bias reduce the internal validity of a study and occurs due to the composition of our study population[29]. Due to the unexpected nature of a

hip fracture obtaining informed consent early after hip fracture is considered problematic and could result in a lower response rate with a higher risk of selection bias[30]. Non-respondents felt too disabled to respond or patients felt overwhelmed by their hip fracture. In **chapter 5** we also included proxy participants (31.0%) in case a patient was unable to participate in this study for several reasons, including cognitive impairment. However these responses may differ, the differences were assumed with random variability rather than systemic bias, and group comparisons using proxy responses are unlikely to be biased[31]. Also selective drop-out is common in longitudinal studies of older adults, because this population have major disabilities and elevated mortality rates[32]. We have more no-show cases in the frail group. Therefore, the QoL and presence of psychological distress in patients after a hip fracture, especially in the frail group, is probably worse than that presented in these studies. To minimize selection bias we used several techniques to increase the response rate and to ensure minimum loss to follow-up, with extensive contact with patients and relatives.

Second, information bias could have affected the validity of our study. We used self-reported questionnaires to screen for psychological symptoms, rather a clinical interview, which is considered as the 'gold standard', was not feasible due to the large sample size of our study.

Third and last, recall bias could have influenced our results. Participants may not accurately recall their status prior to the fracture, which might affect the results of the questionnaires.

Future perspectives

Overall, the findings of this part are of major importance because frailty not only seems to influence patients' postoperative outcomes, such as mortality and complications, but also has a perceived impact on the level of patients' QoL and psychological functioning. Early identification of prefracture frailty in patients with a hip fracture is important for prognostic counseling, (advance) care planning, and the tailoring of treatment.

Future research should measuring frailty status information in hip fracture patients in our daily clinical practice to improve health outcomes. Frail patients might by targeted for interventions to prevent or delay adverse health outcomes and to improve QoL and psychological functioning. Possible strategies to prevent frailty and the effect of frailty interventions, such as exercises, proper nutrition, cognitive

training and multicomponent strategies, should be investigated in patients with a hip fracture.

PART III SOCIETAL IMPACT

Due to aging of the population hip fractures will remain a serious worldwide public health problem. It leads to burden to patients and informal caregivers, and lead to medical consumption, including hospitalizations, and associated healthcare costs. Hip fracture patients belong to one of the larger groups in society that suddenly need informal care for a shorter or longer period. A considerable group of informal caregivers are faced with providing care of greater intensity to hip-fractured patients, and experienced relational, physical and mental health problems **(chapter 7)**. We identified those higher-intensity caregivers, who are largely unrecognized in our healthcare system. The intensity of provided informal care was significantly lower for older patients, patients with dementia, and patients already residing in an institution before the fracture.

However, increasingly stringent cost-containment reforms, in combination with the aging of the population, will lead to a strong increase in the demand for informal care after hip fractures in the Netherlands. Policymakers and healthcare providers should investigate the role of respite programs to improve caregiver QoL by increasing caregiver abilities and confidence to manage daily care challenges in older patients after hip fracture. Furthermore, healthcare providers should give attention to physical- and mental health problems that informal caregivers frequently report.

We provide a comprehensive overview of the burden of illness of hip fractures in an older population in the Netherlands **(chapter 8)**. Compared to two Dutch samples, Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH)[33] and Fracture fixation in the operative management of hip fractures (FAITH)[34], providing costs, we included both intracapsular and extracapsular fractures. Additionally, we included not only patients that were relatively healthy and fit, but 52.1% were considered frail, including patients with dementia or Parkinson's disease. Inherently, the average length of stay in the hospital following the fracture with 8.6 days (HEALTH: 10 days; FAITH: 7 days) and the percentage patients returned home after hospital discharge with 54% (HEALTH: 44%; FAITH: 72%) were between those two studies. In line with these studies, the main determinant in the total costs was related to hospitalizations

and long-term care stay, including a rehabilitation facility or a nursing home. Costs were already found higher in revision surgery patients[33,34]. In the BIOS information about complications and rates of revision surgery after hip fractures were not collected. This has resulted in an underestimation of total costs and QALYs. Already known is the need to carefully select the primary treatment for hip fractures as conversion from internal fixation to arthroplasty is even more costly than primary arthroplasty.

We revealed that QALYs for institutionalized patients were very low and costs for frail patients were significantly higher than for non-frail patients. These results can be used in the FRAIL-HIP study, determining the effect of NOM versus OM of hip fractures in a selected group of frail institutionalized older patients on the QoL, satisfaction of the patient (or proxy) and the caregiver with the management strategy, and health care resource utilization with associated costs, including a cost-effectiveness analysis[16].

Conclusions

This thesis provides outcome information in older and frail patients with a hip fracture, concerning medical decision-making, Quality of Life and societal impact.

The Brabant Hip Fracture Score provide clinicians independent predictors for frail patients at high risk for early mortality, including age, gender, living in an institution, Hemoglobin, respiratory disease, diabetes, malignancy, cognitive frailty and renal insufficiency. Input from Dutch subject-matter experts resulted in a decision-support tool consisted of four items: pre-fracture health status, living in an institution, frailty score, and two or more comorbidities. These two tools provide information to support healthcare providers, patients and relatives in medical decision-making for operative management or palliative care.

We revealed that prefracture frailty is negatively associated with Quality of Life one year after hip fracture. Frailty at onset of hip fracture was the most important prognostic factor of symptoms of depression and anxiety on average in the year following hip fracture. These findings suggest that early identification of prefracture frailty in patients with a hip fracture is important for prognostic counseling, (advance) care planning, and the tailoring of treatment.

We showed that hip fractures lead to a burden to patients, resulting from mortality and (health related)QoL reductions, and to society, considering informal caregivers and (healthcare) costs.

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APPENDICES

Nederlandse samenvatting

Dankwoord / Acknowledgements

Portfolio

List of publications

Curriculum vitae

Een heupfractuur is een ernstige gebeurtenis op oudere leeftijd. Met de stijgende levensverwachting en de daarmee gepaard gaande vergrijzing wereldwijd, lijken heupfracturen een groot probleem te blijven voor zowel het individu als voor de gehele samenleving. Het doel van dit proefschrift is om de uitkomst van ouderen met een heupfractuur te evalueren met betrekking tot: medische besluitvorming **(deel I)**, kwaliteit van leven **(deel II)** en maatschappelijke impact **(deel III)**.

DEEL I: MEDISCHE BESLUITVORMING

Dit deel verschaft informatie aan gezondheidszorgprofessionals, patiënten en naasten in de medische besluitvorming omtrent heupfracturen ten aanzien van keuzes voor operatieve of palliatieve zorg. Dit gedeelte bevat 3 onderzoeksvragen:

- Wat zijn de verschillen in mortaliteit, kwaliteit van leven (KvL), functionele uitkomsten en kosten tussen operatieve en conservatieve behandeling van heupfracturen in ouderen boven de 65 jaar? **(hoofdstuk 2)**
- Wat zijn de beste voorspellende variabelen voor de 30-dagen en 1-jaars mortaliteit in patiënten boven de 65 jaar met een heupfractuur? **(hoofdstuk 3)**
- Welke factoren zijn van invloed op de besluitvorming in de behandeling van kwetsbare ouderen met een heupfractuur? **(hoofdstuk 4)**

Dit deel richt zich op risicoprofielen in oudere patiënten na een heupfractuur om artsen, patiënten en familieleden handvatten te geven voor medische beslisvorming. **Hoofdstuk 2** beschrijft een systematisch literatuuronderzoek en meta-analyse om een overzicht te geven van studies die operatieve met conservatieve behandeling van heupfractuurpatiënten van boven de 65 jaar vergelijken met betrekking tot mortaliteit, (gezondheid gerelateerde) KvL, functionele uitkomsten en kosten. De 30-dagen en 1-jaars mortaliteit was hoger in de conservatieve groep. Geen van de geïncludeerde studies vergeleken (gezondheid gerelateerde) KvL, functionele uitkomsten of kosten tussen de 2 behandelingen. De ongecorrigeerde gepoolde odds ratio (OR) van de 30-dagen en 1-jaars mortaliteit was bijna viermaal hoger in de conservatieve groep. Dit systematisch literatuuronderzoek laat zien dat slechts een paar observationele studies zijn gepubliceerd met een gering aantal heupfractuurpatiënten, die operatief met conservatief beleid hebben vergeleken.

In **hoofdstuk 3** hebben we de Brabant Hip Fracture Score (BHFS) ontwikkeld en intern gevalideerd. We hebben twee gemakkelijk te gebruiken klinische

predictiemodellen voor 30-dagen en 1-jaars mortaliteit ontwikkeld vanuit een cohortstudie met 916 geopereerde heupfractuurpatiënten van 65 jaar en ouder. Onafhankelijke variabelen voor 30-dagen mortaliteit waren: leeftijd, geslacht, woonachtig in een verpleeghuis, hemoglobine gehalte, longziekte, diabetes mellitus en maligniteit. In aanvulling werden cognitieve beperkingen en nierinsufficiëntie geselecteerd in de BHFS-365. Beide modellen laten een acceptabele discriminatie zien na interne validatie (respectievelijke oppervlakte onder de ROC-curve van 0,71 & 0,75) waarbij deze modellen goed passen ($p>0,05$). In de klinische praktijk kan voor de BHFS-30 een afkappunt van ≥24 worden gekozen om kwetsbare oudere patiënten te identificeren met een hoog risico op vroege mortaliteit. Dit kan zorgprofessionals, patiënten en familie ondersteunen bij de medische besluitvorming met betrekking tot gepaste keuzes voor de geschikte behandeling.

In **hoofdstuk 4** gebruiken we een 7-stappen concept mapping methode om factoren te identificeren die van invloed kunnen zijn op de keuze voor een operatief of conservatief beleid in kwetsbare oudere heupfractuurpatiënten. Deze factoren werden vertaald in een keuzehulp die patiënten identificeert die mogelijk geschikt zijn om een conservatief beleid te bespreken. Dit werd gedaan met behulp van data uit de Brabant Injury Outcome Surveillance (BIOS), een multicenter prospectieve observationele cohort studie. De keuzehulp bestaat uit vier items: (1) gezondheidsstatus pre-fractuur; (2) woonachtig in verpleeghuis; (3) mate van kwetsbaarheid; en (4) multimorbiditeit (twee of meer ziekten). De totale score was berekend door het optellen van de vier items met een maximum van vier punten. Een afkappunt van ≥3 is een optimaal afkappunt voor patiënten om de optie van een conservatief beleid te overwegen en te bespreken met zowel de patiënt als zijn of haar naasten.

DEEL II: KWALITEIT VAN LEVEN EN PSYCHOLOGISCHE PROBLEMEN

Dit deel beschrijft de prognostische factoren van KvL en psychologische problemen in heupfractuurpatiënten en bevat 2 onderzoeksvragen:

- Wat is het effect van kwetsbaarheid op KvL in oudere patiënten met een heupfractuur? **(hoofdstuk 5)**
- Wat zijn de prevalentie en prognostische factoren van psychologische symptomen in ouderen met een heupfractuur? **(hoofdstuk 6)**

In **hoofdstuk 5** onderzoeken we het effect van kwetsbaarheid op gezondheidsstatus en KvL in oudere heupfractuurpatiënten. Vanuit de BIOS werden 696 patiënten met een heupfractuur met een leeftijd van boven de 65 jaar geïncludeerd. In geval van cognitieve stoornissen, zoals dementie, werd een naaste geïncludeerd. In totaal werden 371 patiënten (53,3%) als kwetsbaar beschouwd. Kwetsbaarheid was negatief geassocieerd met gezondheidsstatus (β -0,333; 95% betrouwbaarheidsinterval (BI) -0,366 - -0.299), zelf beoordeelde gezondheid (β -21,9; 95% BI -24,2 - -19,6) en welzijn (β -0,296; 95% BI -0.322 - -0.270) in oudere patiënten in het eerste jaar na de heupfractuur. Na het corrigeren voor confounders, inclusief overlijden, gezondheidsstatus pre-fractuur, leeftijd, woonsituatie pre-fractuur, mobiliteit prefractuur, ASA (American Society of Anesthesiologists) classificatie en dementie, zwakte de associatie iets af, maar bleef significant. Hiermee toonden we aan dat kwetsbaarheid negatief is geassocieerd met de KvL het eerste jaar na een heupfractuur.

In **hoofdstuk 6** bepalen we de prevalentie en prognostische factoren voor psychologische problemen na een heupfractuur. Vanuit de BIOS werden 570 patiënten geïncludeerd en de prevalentie van psychologische problemen was 36% na 1 week en 31% na 1 jaar. Kwetsbaarheid ten tijde van de heupfractuur was de meest prognostische variabele voor het ontwikkelen van symptomen van depressie (OR, 2,74; 95% BI 1,41 - 5,34) en angst (OR, 2,60; 95% BI 1,15 - 5,85) gemiddeld genomen over het eerste jaar na een heupfractuur. Kwetsbaarheid was geen prognostische factor voor symptomen van posttraumatische stress (OR, 1,97; 95% BI 0,42 – 9,23). Deze bevindingen suggereren dat vroege identificatie van de mate van kwetsbaarheid ten tijde van de heupfractuur belangrijk is voor het inschatten van de prognose, het plannen van de zorg en de keuze ten aanzien van de behandeling met betrekking tot KvL en psychologische problemen.

DEEL III: MAATSCHAPPELIJKE IMPACT

Dit gedeelte richt zich op de maatschappelijke impact van heupfracturen met betrekking tot mantelzorg en de ziektelast voor de maatschappij.

- Wat is de impact voor mantelzorgers die zorg verlenen aan oudere patiënten met een heupfractuur? **(hoofdstuk 7)**
- Wat is in Nederland de ziektelast van heupfracturen in een oudere populatie? **(hoofdstuk 8)**

In **hoofdstuk 7** onderzoeken we de taken, intensiteit en de zorg-gerelateerde KvL van de mantelzorger voor ouderen met een heupfractuur binnen de eerste 6 maanden. In deze cross-sectionele studie met data van de heupfracturen uit de BIOS hebben we mantelzorgers geïnterviewd ten aanzien van de verleende mantelzorg op 1, 3 of 6 maanden na de heupfractuur. In totaal werden 123 primaire mantelzorgers geïncludeerd. De CarerQoL-7D score was gemiddeld 83,7 (SD 15,0) na 1, 3 en 6 maanden. Er waren geen grote verschillen tussen de verschillende meetmomenten. De gemiddelde geïnvesteerde hoeveelheid mantelzorg betrof 39,5 uur per week gedurende 6 maanden. Partners van patiënten met een heupfractuur verstrekte de meeste uren mantelzorg (β 34,0; 95% BI: 20.9 - 47,1). Vrouwelijke mantelzorgers hadden een lagere zorg-gerelateerde KvL (β -7,8; 95% BI: -13,3 - -2,3) en hadden een driemaal hogere odds op relationele problemen (gecorrigeerde OR 3,02; 95% BI 1,08 – 8,43). Mantelzorgers die op 6 maanden mantelzorg verleenden hadden meer fysieke gezondheidsklachten (gecorrigeerde OR 2,54; 95% BI 1,05 – 6,14). Een behoorlijke groep mantelzorgers ervoeren relationele, fysieke en mentale gezondheidsproblemen ten gevolge van het verlenen van mantelzorg gedurende de eerste 6 maanden aan naasten met een heupfractuur.

Hoofdstuk 8 onderzoekt de ziektelast van de heupfracturen in een oudere Nederlandse populatie op een aantal meetmomenten na behandeling. Vanuit de BIOS werden patiënten van 65 jaar en ouder met een heupfractuur geincludeerd. De iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) werden gebruikt. De gezondheidsstatus was significant verminderd vergeleken met de situatie van voor de heupfractuur en patiënten herstelden binnen 1 jaar niet tot hun niveau van vóór de heupfractuur. De gemiddelde waarde van de kwaliteit van de levensjaren (QALY) was gedurende 1 jaar follow up 0,528 (95% BI: 0,504 - 0,553). De totale kosten in het eerste jaar na heupfractuur was gemiddeld €27.573. QALYs waren significant hoger voor patiënten die niet als kwetsbaar werden beschouwd (gemiddeld 0,725; 95%BI: 0,701 - 0,749 versus 0,348; 95% BI: 0,318 – 0,379). QALYs voor patiënten uit een verpleeghuis waren zeer laag met een waarde van 0,264 (95% BI: 0,220 - 0,308). Kosten voor kwetsbare patiënten (gemiddeld €33.942; 95% BI: €27.623 - €40.260) waren hoger dan voor niet-kwetsbare patiënten (gemiddeld €16.044; 95% BI: €11.837 - €20.250).

Deze studies geven aan dat heupfracturen lijden tot een ziektelast voor zowel patiënten, resulterend in overlijden en vermindering in (gezondheid gerelateerde) KvL, als voor de maatschappij, met betrekking tot mantelzorg en (gezondheidszorg) kosten.

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PHD PORTFOLIO

Name PhD student: Cornelis Leendert Pieter van de Ree
PhD period: May 2015 – April 2018
Promotor Prof. dr. J.A. Roukema
Co-promotor: dr. M.A.C. de Jongh & dr. T. Gosens

1. PhD training	Year
General courses	
Scientific writing in English for publication in Biomedical Journals, ASZ, Dordrecht, NL	2015
Good Clinical Practice, ETZ, Tilburg, NL	2015
Systematic review and meta-analysis, Tilburg University, Tilburg, NL	2015
Academic Visualisation Workshop, Tilburg University, Tilburg, NL	2015
Master's Programme in Epidemiology, EpidM, Department of Epidemiology and Biostatistics, VU Medical Center, NL	
Epidemiological survey: design and interpretation	2015
Principles of epidemiologic data-analysis	2015
Regression analysis	2015-2016
Clinimetrics: Assessing measurement properties of health measurement instruments	2016
Practical epidemiology: study protocol	2016
Recommendation in methodology	2017
Clinical prediction models	2016
Multilevel analysis	2017
Longitudinal data-analysis	2017
Missing data: consequences and solutions	2017
Seminars and workshops	
Fragility Fracture Network Global Congress, Rotterdam, NL	2015
Nat. Wetenschapsagenda (NWA), Gezondheidszorgonderzoek, preventie en behandeling, Ede, NL	2016
Symposium Geriatrische Traumachirurgie, 's-Hertogenbosch, NL	2016
The use of Patient Reported Outcome Measures in healthcare, Zorginstituut, Nijmegen, NL	2017
Oral presentations (inter)national conferences	
Xperiment Trauma/Neuro meeting, Tilburg, NL	2016-2017
Wetenschapsdag ETZ, Tilburg, NL	2016-2017
Trauma TopZorg symposium: "Het ongeval op de oude dag. Tot hoe ver gaan we?" ETZ, Tilburg, NL	2016
International Society for Quality of Life Research (ISOQOL), Copenhagen, Denmark	2016
European Congress of Trauma & Emergency Surgery (ECTES), Bucharest, Romania	2017
Trauma TopZorg Symposium: "Bruggen bouwen. Buitengewone Traumazorg.", ETZ, Tilburg, NL	2017
Regionale OpleidingsGroep Orthopedie (ROGO), Rotterdam, NL	2017
Jaarcongres Nederlands Orthopaedische Vereniging (NOV), 's-Hertogenbosch, NL	2018
Nordic Orthopaedic Federation Congress, Reykjavik, Iceland	2018
International Society for Quality of Life Research (ISOQOL), San Diego, United States	2019
Poster presentations (inter)national conferences	
Trauma TopZorg symposium, Tilburg, NL	2015
Traumadagen, Amsterdam, NL	2016, 2019
European Hip Society Congress, Den Haag, NL	2017

2. Teaching	Year
Interns – Bachelor / Master Medicine / Psychology	2016-2018

LIST OF PUBLICATIONS

van de Ree CLP, de Munter L, Biesbroeck BHH, Kruithof N, Gosens T, de Jongh MAC.
The prevalence and prognostic factors of psychological distress in older patients with a hip fracture. A longitudinal prospective cohort study;
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Kruithof N, Polinder S, de Munter L, **van de Ree CLP**, Lansink KWW, de Jongh MAC; BIOS-group.
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Kanters TA, **van de Ree CLP**, de Jongh MAC, Gosens T, Hakkaart-van Roijen L. Burden of illness of hip fractures in elderly Dutch patients.
Arch Osteoporos. 2020 Jan 3;15(1):11. doi: 10.1007/s11657-019-0678-y.

de Munter L, Polinder S, Haagsma JA, Kruithof N, **van de Ree CLP**, Steyerberg EW, de Jongh M.
Prevalence and Prognostic Factors for Psychological Distress After Trauma.
Arch Phys Med Rehabil. 2020 May;101(5):877-884. doi: 10.1016/j.apmr.2019.10.196.

Joosse P, Loggers SAI, **van de Ree CLP**, van Balen R, Steens J, Zuurmond RG, Gosens T, van Helden SH, Polinder S, Willems HC, Van Lieshout EMM; FRAIL-HIP study group.
The value of nonoperative versus operative treatment of frail institutionalized elderly patients with a proximal femoral fracture in the shade of life (FRAIL-HIP); protocol for a multicenter observational cohort study.
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Effect of frailty on quality of life in elderly patients after hip fracture: a longitudinal study.
BMJ Open. 2019 Jul 18;9(7):e025941. doi: 10.1136/bmjopen-2018-025941.

de Munter L, Polinder S, **van de Ree CLP**, Kruithof N, Lansink KWW, Steyerberg EW, de Jongh MAC.
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Kruithof N, Haagsma JA, Karabatzakis M, Cnossen MC, de Munter L, **van de Ree CLP**, de Jongh MAC, Polinder S.
Validation and reliability of the Abbreviated World Health Organization Quality of Life Instrument (WHOQOL-BREF) in the hospitalized trauma population.
Injury. 2018 Oct;49(10):1796-1804. doi: 10.1016/j.injury.2018.08.016.

Stavenuiter R, Hermanusen H, **van de Ree CLP**, Steens J.
Oudere breekt heup, opereren of niet?
De Kwestie, Medisch Contact, 9 augustus 2018; https://www.medischcontact.nl/opinie/de-kwestie/kwestie/oudere-breekt-heup-opereren-of-niet.htm

van de Ree CLP, De Jongh MAC, Peeters CMM, de Munter L, Roukema JA, Gosens T.
Hip Fractures in Elderly People: Surgery or No Surgery? A Systematic Review and Meta-Analysis.
Geriatr Orthop Surg Rehabil. 2017; Sep;8(3):173-180. doi: 10.1177/2151458517713821.

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J Patient Rep Outcomes. 2017;2(1):23. doi: 10.1186/s41687-018-0048-3.

Peeters CMM, Visser E, **van de Ree CLP**, Gosens T, den Oudsten B, de Vries J. Quality of life after hip fracture in the elderly: A systematic literature review
Injury. 2016 Jul;47(7):1369-82. doi: 10.1016/j.injury.2016.04.018

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Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: the Brabant Injury Outcome Surveillance (BIOS) study
Inj. Prev. 2016;0:1-9. doi:10.1136/injuryprev-2016-042032

CURRICULUM VITAE

Marc van de Ree was born on the 6th of February 1988 in Hendrik-Ido-Ambacht, the Netherlands. In 2006 he graduated from secondary school at DevelsteinCollege Zwijndrecht. In the same year he started medical school at the Erasmus University Medical Center Rotterdam. He attended a minor of orthopaedic and trauma surgery in Talegaon and Pune in India. In 2008 he became a member of “het snijzaalteam” and participated as tutor in a peer-to-peer surgical anatomy masterclass (Erasmus Anatomy Research Project) led by prof. dr. G.J. Kleinrensink (department of anatomy). After graduation in 2012, he started his medical career consecutively in general surgery at the St. Elisabeth Hospital in Tilburg and in orthopaedic surgery at the Albert Schweitzer Hospital in Dordrecht. In 2015 he started as a PhD fellow under supervision of prof. dr. J.A. Roukema, dr. M.A.C. de Jongh and dr. T. Gosens at Trauma TopZorg in Elisabeth-TweeSteden Hospital in Tilburg. In 2018 he graduated from master’s programme in Epidemiology at the VU Medical Center Amsterdam and in the same year he started with his orthopaedic surgery training. He worked as a resident general surgery in the Albert Schweitzer Hospital in Dordrecht (dr. P.W. Plaisier). In 2019 he started his residency for orthopaedic surgery in Elisabeth-TweeSteden Hospital (dr. T. Gosens) and in 2021 he will continue his residency in Erasmus Medical Center Rotterdam (dr. P.K. Bos).

In addition to his clinical work he participates in the Dutch Frail Hip study, a co-operation with trauma surgeons, geriatricians, elderly care physicians and orthopeadic surgeons to research the value of nonoperative treatment in frail institutionalized elderly patients with a hip fracture.

He lives with his wife, Claire, in Rotterdam, and in his spare time he enjoys to cycle, to sail, and to do mountain sports.