Master's thesis

NTNU
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The burden of hip fractures in elderly patients: Changes in health-related quality of life one year following hip fracture

Master's thesis in Clinical Health Science - Applied Clinical Research
Supervisor: Pernille Thingstad
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Abstract

Background: The impact of a hip fracture on quality-adjusted life years has not been thoroughly studied in Norwegian hip fracture patients. The aim of this study was to 1) quantify the change in health-related quality of life the first year following hip fracture, and 2) investigate which pre-fracture factors are associated with the change in HRQoL.
Material and Methods: Longitudinal cohort study including 387 hip fracture patients. Data on HRQoL was obtained using the EQ-5D-3L questionnaire at 1-, 4-, and 12-months post fracture. Pre-fracture data on HRQoL were estimated using a published mapping algorithm and data from the Barthel Index, and a published constant was used as a proxy for data on HRQoL immediate post-fracture period. QALYs were calculated using the area under the curve method. Multivariate regression analysis was performed to investigate predictors of QALY loss.
Results: Mean pre-fracture HRQoL for all participants was 0.64. HRQoL declined to 0.27, 0.44, 0.51 and 0.53 immediately after fracture, 1-. 4-, and 12-months post fracture, respectively. The mean loss in QALY was 0.15. Pre-fracture HRQoL, pre-fracture ADL and present comorbidities were predictors of the QALY loss.
Conclusions: A hip fracture has a dramatic impact on the patients´ HRQoL, and the deterioration sustained one year after the fracture. The QALY loss represents a substantial impact on these patients in terms of poor HRQoL and premature mortality. Our findings emphasize the importance of preventing hip fracture and optimizing both pre- and postoperative care in order to prevent loss of QALYs.

Relevance

This thesis will contribute to the existing literature in the field of HRQoL among elderly hip fracture patients and provide new insights into the problem of collecting pre-fracture data in this population. Knowledge about morbidity and mortality, and thus QALYs is of direct interest for each individual sustaining a hip fracture and for the society as a whole in terms of societal burden and priority setting. Moreover, the results will convey valuable information for future research.

Acknowledgements

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Last, I would like to thank my husband for always believing in me and supporting me. Without your faith in me I am not sure I would have had the courage to finish this project. And to my boys, Frederik and Aksel, for your impatience and for always reminding me of the important things in life. And yes, mommy is done with her homework now.

Abbreviations

ADL – Activities of Daily living (i-ADL/p-ADL)

HRQoL – Health-Related Quality of Life

QALY – Quality-Adjusted Life Year

ICUROS – International Cost and Utility Related to Osteoporotic Fractures Study

NICE – National Institute for health and Care Excellence

CGC – Comprehensive Geriatric Care

PROM – Patient-Reported Outcome Measure

HS – Health State

QOL – Quality of Life

TTO – Time Trade-Off

VAS – Visual Analogue Scale

BI – Barthel Index

NEADL – Nottingham Extended Activities of Daily Living

CDR – Clinical Dementia Rating scale

ICD – International Classification of Diseases

THFT – Trondheim Hip Fracture Trial

ED – Emergency Department

NCoDR – Norwegian Cause of Death Registry

MCAR – Missing Completely at Random

AUC – Area Under Curve

SD – Standard Deviation

CI – Confidence Interval

CI – Cognitive Impairment

Background

Introduction

Hip fracture is a global public health problem. Worldwide, there are 1.3 million hip fractures each year, associated with over 700 000 deaths (1). The cost of this is estimated to 1.4 % of the total healthcare burden in established market economies (1), with acute and post-acute institutional care as the primary driver (2). The highest incidence rates of hip fractures are found in the Scandinavian countries, and there is evidence of incidence rates being higher among women and increasing with age (3). Analysis indicates a decline in the incidence of hip fractures. However, an increase in the prevalence is expected in the years to come due to the aging of population (4). By year 2025, the number of hip fractures is estimated to approximately double to 2.6 million (5). Estimates indicate that by 2050, 20 % of the Norwegian population will be 70 years old or older, compared to 12 % today (6). This population growth will increase the population at risk for hip fracture and potentially the health and economic burden of hip fractures.

A hip fracture is a dramatic and highly debilitating event for many patients. After a fracture, both short-term and long-term outlooks for patients are generally poor, with increased 1-year mortality up to 30% (2, 7) and an estimated 25 % reduction in life expectancy (8). Further, hip fractures are associated with significant morbidity with severe pain (9), negative effects on mobility (7, 10, 11) and activities of daily living (ADL) (7, 10-12), and increased risk for need of long-term care (10). In recent years, a growing number of studies on health-related quality of life (HRQoL) in hip fracture patients have been published and the substantial negative impact of a hip fracture on HRQoL is well established (9, 13-17).

The burden of hip fractures is twofold, as fractures affect both the health of individuals and societal costs. In order to quantify the burden of disease and facilitate rational decision-making for resource allocation, it is important to estimate the impact of a disease or an injury using measures that can be compared across diseases (18). Although several studies have investigated the impact of hip fracture on mortality and morbidity, only few studies have estimated the impact on quality- adjusted life years (QALYs) (19). The International Cost and Utility Related to Osteoporotic Fractures Study (ICUROS) is one of few studies estimating accumulated QALY loss in fragility fractures, including hip fracture. The 12-months accumulated QALY loss in hip fracture patients were estimated between 0.21-0.34 for

different countries (13, 16, 17). This was the highest accumulated QALY loss of the fragility fractures studied (17). Further, factors associated with loss of QALYs are poorly examined. For patients sustaining a hip fracture, the only factors identified being associated with loss of QALYs is higher pre-fracture HRQoL and higher age (16, 17). Country-specific studies and broader examination of associated factors have been recommended for further research (19).

Aims of the master´s thesis

1. The primary aim of this study is to quantify the change in patient reported HRQoL the first year after sustaining a hip fracture in a cohort of elderly patients in Trondheim, Norway. The change in HRQoL will be expressed in terms of QALYs.
2. A secondary objective is to investigate which pre-fracture characteristics and factors are associated with the change in HRQoL the first 12 months following a hip fracture.

Theoretical framework

Epidemiology of hip fractures in Norway

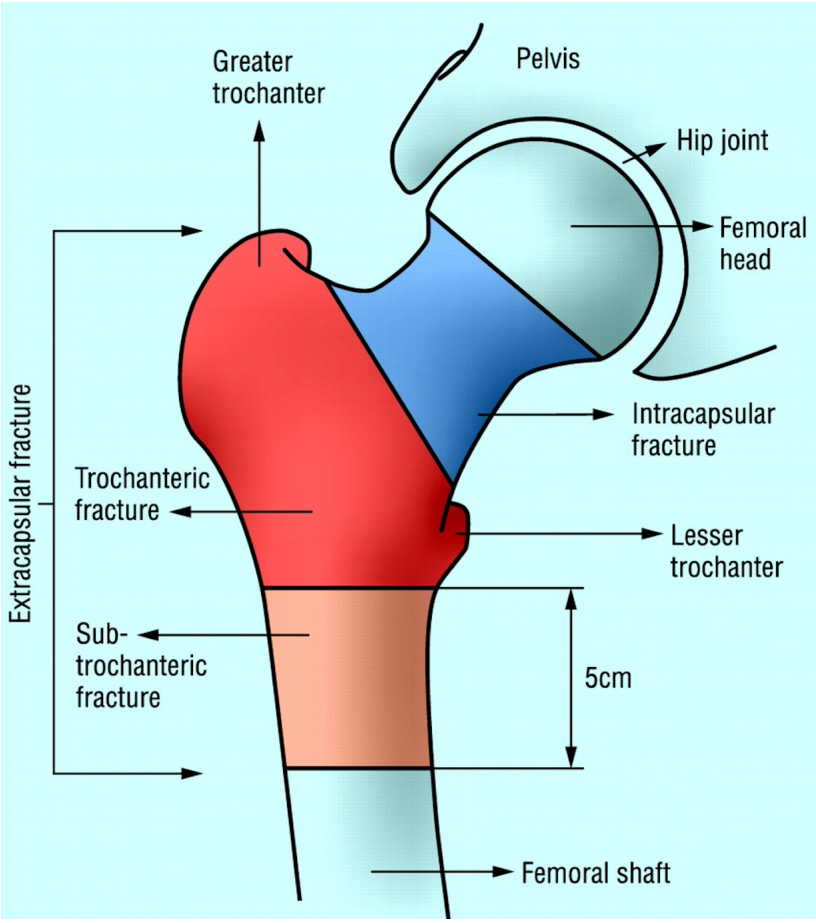
Norway has one of the highest incidences of hip fractures in the word, and every year approximately 9000 persons are operated for a hip fracture (3, 20). It is estimated that for people over 50 years of age, the early incidence of hip fractures is 76-82 per 10 000 for women and 35-39 per 10 000 for men in Norway (21). According to the Norwegian Hip Fracture Hip registry Norwegian hip fracture patients are on average 83.2 years old, over 70% are female and the majority of hip fracture patients have several comorbidities (22).

Osteoporosis, tendency to fall, old age, Alzheimer`s disease and use of anxiolytic or hypnotic drugs are known risk factors for hip fracture (23-25). There is also a high risk of sustaining a hip fracture, if the person has had a previous fragility fracture or hip fracture (26).

Classification of hip fractures

A hip fracture is a fracture near the hip joint, only affecting the femur. It is often classified according to the anatomical location. Fractures of the proximal femur are classified as intra- and extracapsular fractures. Intracapsular are divided into displaced and non-displaced fractures depending on the angle of the fractures proximal part of the femur and the dislocation of the fragment. Extracapsular are fractures in the trochanter region or the sub-trochanter region comprising of the 5 cm area distal to the lesser trochanter in the femur. Trochanter fractures may be stable or unstable, often comminuted. Sub-trochanter fractures are often unstable and the prognosis is poor with increased risk of a profound and lasting deterioration of musculoskeletal function in addition to a substantial negative impact on HRQoL (27).

Figure 1 Classification of hip fractures. Fractures in the blue area are intracapsular and those in the red and orange areas are extracapsular (28).



Treatment of hip fractures

Early surgery is the state of the art in hip fracture treatment. The National Institute for Health and Care Excellence (NICE) guidelines recommend surgery within the first 36-48 hours after sustaining a hip fracture (29, 30). Others advocate even earlier surgery (6-12 hours) to minimize possible complications and even mortality (31).
The use of surgical procedure depends on the type and location of the hip fracture (29).

Comorbidities significantly impact the patients' outcome after hip fracture (22, 32, 33). Preoperative examination and assessment are required to determine patients' baseline medical conditions and identify decompensated or previous unrecognized conditions (34, 35). This suggests that older people who sustain hip fractures are frail, and especially vulnerable and

high risk of functional decline caused by inability to respond adequately to the strain the injury represents. Comprehensive geriatric care (CGC) is a multidimensional and multidisciplinary approach targeting frailty. CGC includes diagnostics and treatment of comorbid conditions, prevention and treatment of complications such as delirium and infections, systematic review of medications, prevention and treatment of nutrition failure, assessment and treatment of pain and fall risk, assessment of ADL and mobility, and with emphasis of early mobilization and participation in ADL activities and early discharge planning (35).

The benefit of CGC for hip fracture patients have been clearly demonstrated with better mobility, fewer hospital days, increased survival and better HRQoL for patients receiving CGC in comparison to standard orthopedic care (34-39).

Outcomes after hip fracture

Mortality

Mortality following hip fracture is high and well reported in several clinical studies. In general, 30-days mortality is described between 10% and 13 % and 1-year mortality is described between 22 % and 33% (40-42). Several studies have investigated long-term mortality after hip fracture, indicating an excess mortality in this population (43-45). A Dutch study of elderly hip fracture patients found that the 5-year mortality incidence after hip fracture was almost 70 %, compared to 22.9% for the general Dutch population (46). Male gender, high age, low BMI, comorbidities, chronic cognitive impairment, and nursing home residency have been established as risk factors for short-term death in hip fracture patients (32, 47-49). Excess mortality is not fully explained by poor prefracture health status, indicating that some mortality risk is related to the fracture itself (34).

Mobility and ADL-function

A hip fracture has a substantial negative impact on patients' mobility, ambulatory status and functioning in activities of daily life (ADL) (7, 10-12). According to a Norwegian study, the proportion of patients walking without any aid decreased from 76 % to 36 % after a hip fracture, and 43 % of the patients lost their pre-fracture ability to move outside their own homes (11). Another study found that 25% of survivors are bedridden or in wheelchair one

year after sustaining a hip fracture (44). This impairment is long lasting with a review of long-term disability in patients with hip fractures estimating that 42 % of survivors do not recover to their pre-fracture mobility (10). As many as 60 % of hip fracture patients need assistance in their personal ADL one year after hip fracture, and a decline of 13% for the personal ADL is found within the same period (44). Furthermore, 93 % need help with bathing, at least 45 % with grooming and 66 % are dependent with eating. These negative effects on functional status and ability to perform ADL leads to increased dependence and change in residential needs (2, 7, 10, 11). In terms of residency, about 20 % of patients being community-dwelling at the time of fracture enters a long-term care facility the first after a hip fracture (10).

HRQoL

Several studies have established the negative impact of hip fracture on HRQoL (9, 12, 13, 15, 16). Already before sustaining a hip fracture, this population shows signs of having impaired HRQoL (13, 14, 16). This is seen in correspondence to most older hip fracture patients being frail, having pre-existing comorbidities and showing a functional deterioration that is typical for geriatric patients (50). HRQoL is considerable reduced after a hip fracture and the deterioration sustains the first-year post fracture. The deterioration in HRQOL is present irrespective of age and type of fracture (9), and the lowest values of HRQoL is seen in the subgroups of patients > 80 years and with cognitive impairment (15). HRQoL improves with time from fracture, however, one year after sustaining a hip fracture, the vast majority does not attain their pre-fracture level of HRQoL (13-16).

Compared to pre-fracture status, the proportion of patients reporting problems at four months more than doubles in terms of mobility, self-care, usual activities, and pain/discomfort, indicating that these are the most affected dimensions of HRQoL after a hip fracture (9). At one year post fracture, there is still a marked increase of patients reporting on problems in these dimensions compared to pre-fracture.

Established predictors of poor HRQoL one year after hip fracture are cognitive impairment, extracapsular fracture, and higher age (9, 22, 51).

Patient-Reported Outcome Measures (PROMs)

Traditionally, the focus of outcome for hip fracture patients has been on clinical outcomes such as mortality and surgical implant success (52). There is an increasing recognition of the need to diversify outcomes for this patient group. The last decades there has been an increase in the use of patient-reported outcome measures (PROMs).

PROMs are defined as standardized, validated questionnaires completed by patients to measure their perceived HRQoL (53). PROMs are often argued to be the outcome of most significance to patients (54).

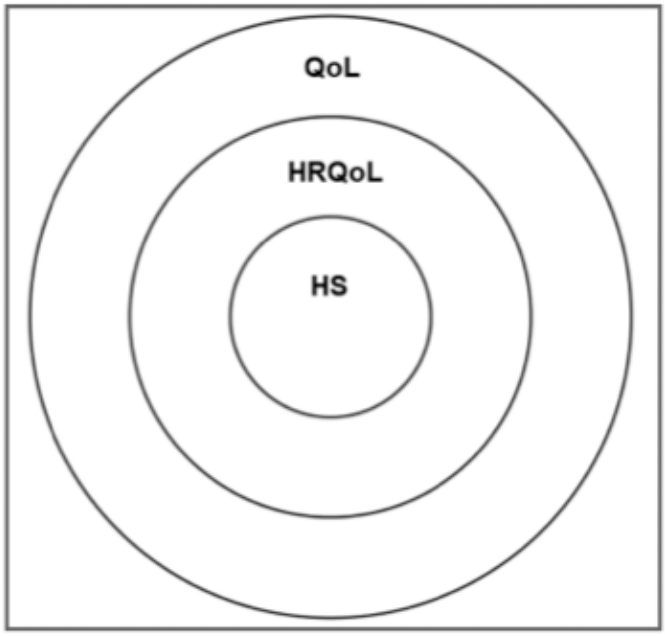
PROMs are designed to be either generic or condition specific (55). Condition-specific PROM questionnaires are used to identify symptoms and severity within specific conditions and diseases. These questionnaires have the advantage to detect small changes in health- or functional status but does not allow for comparison between different conditions. Generic PROM questionnaire does not focus on the impact of a particular condition or disease. Rather, it considers a broad range of dimensions of HRQoL that, in principle, could be impacted by any disease. Further, the generic PROMs can be divided into health profiles and preference based. Health profiles can provide descriptive information about patients' condition and can be used as a measure of efficacy in interventions but are not weighted on people's preferences. The characteristic of the preference-based PROM is that for every described health condition, they give a weighted score calculated in terms of how people value the various health conditions. Such a weighted score is called index score and is often rated on a scale of 0 to 1, where 0 is "worst possible health condition" and 1 is "best imaginable health condition". Generic preference-based instruments have the advantage that they make it possible to compare health improvements or deteriorations across diagnoses and can be used to calculate QALYs.

Health-related Quality of Life (HRQoL)

The terms health status (HS), health-related quality of life (HRQoL) and Quality of Life (QoL) are often used interchangeably. Confusion remains in the literature about the meaning of these terms and little agreement exists on their definitions (56). These are all self-reported (i.e subjective) and multidimensional assessing at least three domains: physical,

psychological, and social functioning. The term HRQoL narrows QoL to aspects relevant to health. However, HRQoL is a comprehensive and complex concept for which no universally accepted definition is available (57). HRQoL is described as a multidimensional concept that provides insight into an individual's perceived health (58). Differences in perception account for the fact that people with the same objective health status can report their HRQoL very differently (59). Measures of HRQoL provide a comprehensive assessment of the burden of preventable and chronic diseases, injuries, and disabilities (60). Administratively, HRQoL measures provides data for financial allocation, quality control, and policy development (58).

Figure 2 Conceptualisation of Quality of Life (QoL), Health-Related Quality of life (HRQoL) and health status (HS).

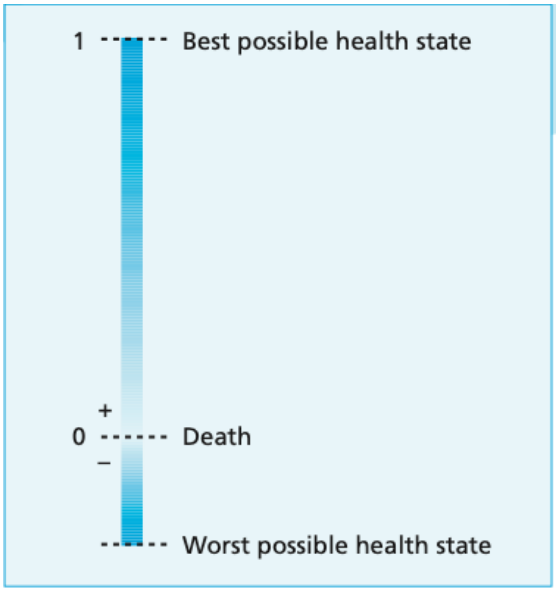


The EuroQol EQ-5D-3L instrument

EQ-5D-3L is a standardized measure of HRQoL and was introduced in 1990 by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economical appraisal (61). EQ-5D-3L is designed for self-completion, hence, a patient reported outcome measure (PROM). EQ-5D-3L is validated in more than 180 languages and in various modes of administration, e.g., face-to-face or telephone interview administration. The EQ-5D -3L is the recommended and most widely used instrument for measuring HRQoL in economic evaluations (62).

The EQ-5D-3L descriptive system comprises the following five dimensions*: mobility, self-care, usual activities, pain/discomfort,* and *anxiety/depression*. Each dimension has 3 levels of response: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. The decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state (for example, health state 11223 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety and depression). A total of 243 (3^5) possible health states are defines in this way for the EQ-5D-3L, to which "unconscious" and "dead" are added to make 245 in total. EQ-5D-3L health states may subsequently be converted into a single summary number (index score), which reflects how good or bad a health state is according to the preferences of the general population of a country/region (61). Value sets have been generated using the time trade-off (TTO) valuation technique (63). The index score represents the valuation attached to each health state on a continuum between 0 and 1, where 0 is equivalent to being dead and 1 represents best possible health state, although some health states are regarded as being worse than death and have negative valuations (See figure 3). The EQ-5D-3L index score ranges from –0.594 to 1 (a low score suggests a worse HRQoL).

Figure 3 Health state valuations – index score.



To this date there is no value set available based on the preference of the Norwegian population. In the absence of a country-specific value set, the preferences of the UK general

population are recommended by the EuroQol Group reflecting that it is considered most robust and often used in clinical studies to allow for comparison (64-66).

There are evidence of a possible ceiling effect using the EQ-5D-3L. Especially when used in general population surveys, but also in some patient populations (53). However, when used in an unselected hip fracture population the EQ-5D-3L has shown discriminatory ability, high content validity and responsiveness to change (19, 64, 67-71). In Norway, the EQ-5D-3L is the recommended instrument for calculating QALYs (72).

There is no consensus on the minimally important clinical difference for the EQ-5D-3L index score. However, on the patient level, changes of approximately ± 0.12 have been reported to equate clearly improved and clearly deteriorated functional status after hip fracture (73).

Quality-adjusted life years (QALYs)

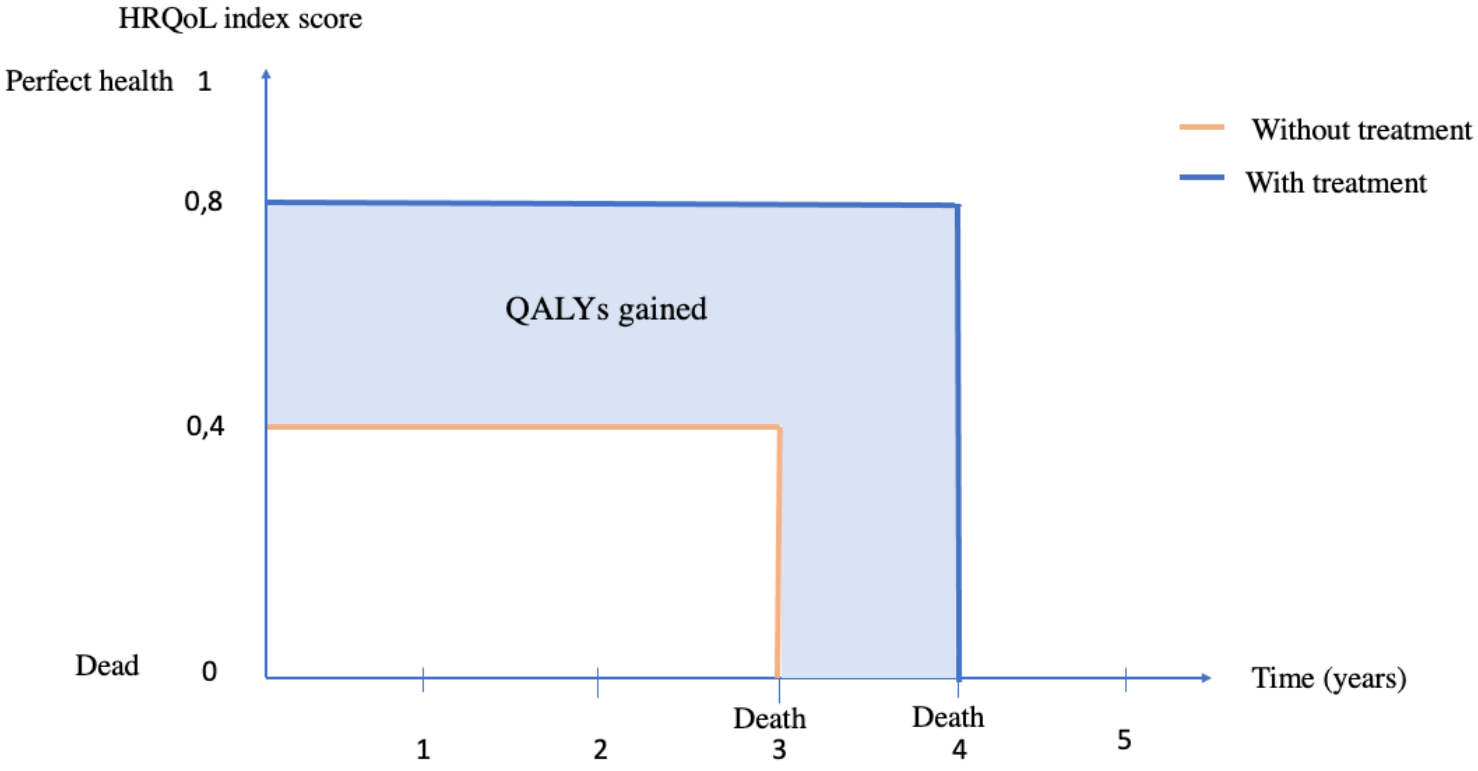
The concept of QALY was first introduced in 1968 by Herbert Klarman and colleagues in a study on chronic renal failure (74). The National Institute for Health and Clinical Excellence (NICE) defines QALY as a "measure of a person's length of life weighted by a valuation of their HRQoL"(75). The QALY is commonly used in health economic evaluations as a means of quantifying the health effect of a medical intervention or a prevention program and ultimately to help payers allocate healthcare resources (76).

Although QALYs is most frequently used for measuring health improvements (QALYs gained), it can also be used to quantify the burden of disease or injury (QALYs lost). QALY is an attractive outcome measure in studies of hip fracture patients because it offers the advantage of capturing at the same time, and in one metric, the impact on both mortality and morbidity (18). QALY loss provides a measure of the health gap experienced by hip fracture patients compared to the normal population and provides an estimate of the health loss that could be avoided if a hip fracture was prevented. Such information is important when making assessments of severity.

One QALY equals one year in perfect health. The number of QALYs is found by multiplying the HRQoL index score (measured by a generic, preference-based PROM) with the duration

of the HRQoL index score. Further, QALYs gained/lost can be calculated from the difference of two trajectories (see figure 4). E.g., if the difference in QALYs between the two trajectories is 2, then this is equivalent to a gain/loss of 2 QALYs, which is equivalent to a gain/loss of 2 years in full health.

Figure 4 Example of QALY gain. The orange line represents a patient that without treatment of a given disease that has a HRQoL index score of 0.4 over 3 years (0.4 x 3 =1,2 QALYs). The blue line represents the same patients that with treatment experiences a HRQOL index score of 0,8 for 4 years (0.8 x 4= 3,2 QALYs). The QALYs gained due to better HRQoL, and prolonged lifespan (blue shaded area) is 3,2-1,2 = 2.



Severity of illness and priority setting

A socio-economically correct allocation of resources in the health care system is the one that maximizes the population's health, e.g., expressed as QALYs. The resources are limited, and it will always be necessary to prioritize between different health measures. Priority setting is one of several policy tools to ensure equity in the access to health care services, and thus concerns the distribution of health care services.

There are four types of decisions for which prioritization is relevant: 1) decisions in clinical practice, 2) decisions regarding distribution of a limited budget between different types of health care services, 3) decisions regarding introduction of new medications, treatment options, diagnostic techniques, public health care programs, i.e. decisions relating to changes in capacity; 4) political decisions at the societal level regarding allocation of resources among various types of public and health care services.

Severity of illness has been a criterion for priority setting in the health care sector in Norway since 1987 (77), and assessment of severity is relevant for priority setting at all levels in the health care sector. The severity of the condition is to be assessed based on; 1) the risk of death or loss of function; 2) the degree of loss of physical and mental function; and 3) pain, physical or mental distress. In priority setting in Norway, severity is operationalized as absolute shortfall, i.e the number of QALYs lost as a result of premature death and reduced HRQoL during the period of illness. Absolute shortfall is equivalent to future loss of QALYs and expresses the number of QALYs lost by a patient group as a result of a disease as compared with the average expected QALYs for the population of the same age.

In the discussion on the use of severity as a criterion for priority setting, the relationship between the severity criterion and age has been a topic of particular debate.

Assessment of pre-fracture HRQoL

Insight into the change from pre- to post-fracture HRQoL of hip fracture patients is important to derive estimates of the impact of the hip fracture on HRQoL and QALYs. Prospectively collected pre-fracture data are, however, often not available due to the difficulty to collect these data before the hip fracture occurs. Current methods assessing pre-fracture HRQoL consists mostly of retrospective recalled data, showing consistently higher pre-fracture HRQoL scores than population norms, implying a systematic overestimation of the change in HRQoL and thus QALYs gained/lost (78). Thus, there is a need to investigate alternative methods for collecting pre-fracture data in patients sustaining a hip fracture.

Material and Methods

Setting and participants

This is a longitudinal cohort study based on secondary analysis of data from the Trondheim Hip Fracture Trial (THFT). THFT was a randomized controlled trial and has been reported in full previously (34-36).

The target population was older community-dwelling hip fracture patients. Inclusion and exclusion criteria are presented in Table 1.

Table 1 Inclusion and exclusion criteria for the THFT

Inclusion criteria	**Exclusion criteria**
• Confirmed intracapsular, trochanteric or subtrochanteric fracture (ICD-10, 72.0-72.2) • Age > 70 • Community-dwelling at time of the fracture • Living in the catchment area (City of Trondheim and the nearest municipalities) • Able to walk 10m prior to the fractur • Able to give informed consent	• Life expectancies shorter than 3 months • Pathological fracture • High energy trauma

For this master´s thesis we included patients with registered pre-fracture data on the Barthel Index.

Recruitment and inclusion

In THFT all participants were recruited at the Emergency Department (ED) at St Olavs hospital, the University Hospital of Trondheim, between April 2008 and December 2010.

Data collection

Background information on living conditions, cognitive function, and ADL-function before the fracture; pre-fracture BI, NEADL, CDR, and other background characteristics were collected from all patients starting already during the stay at the emergency department and completed at day 3 or 5 at the allocated clinical ward. Data on previous and present co-morbidity was collected from hospital records. The postoperative follow-up with longitudinal assessment of HRQoL were performed by trained interviewers (health professionals) at site where the patients was living at 1 month, and at the hospital out-patient clinic at 4 and 12 months. Patients who were not able to come to the out-patient clinic due to deteriorated health state at the 4- and 12 months follow-up were sought out and interviews at site where they were living.

Data of death were registered one year after fracture and were collected from the Norwegian Cause of Death Registry (NCoDR). Whenever possible during data collection, patients were the primary informant. This exception was for CDR scores, which were collected from proxies (next of kin) by telephone for all patients, and scores for the BI and the NEADL scale, which were collected from proxies by telephone for 10-20 % of patients who were unable to provide data.

To reduce the risk of absence and missing data, extensive measures were taken in THFT. The trial had a particular focus on practical routines to ensure data of good quality. This was a conscious strategy considering the old and frail population of the study.

In THFT, missing data on the EQ-5D-3L were considered not to be missing completely at random (MCAR). It was assumed that the cognitive and physical status of the patient affected the probability of missing. Multiple imputations (m=100) were performed where the EQ-5D-3L Index score were missing. The imputation model was restricted to predict values inside the possible range, *i.e.,* values between -0.594 and 1 for the EQ-5D-3L. The imputation model is described in full previously (34). For this thesis, the number of missing values on the EQ-5D-3L questionnaire was 37 (9.6%), 30 (7.7%) and 32 (8.3%) at 1-, 4- and 12-months post fracture.

Measures of HRQoL and QALY

Measures of HRQoL at one, four and 12 months post fracture was obtained using the Norwegian version of EQ-5D-3L (79). The UK time trade off preference value was used to

calculate HRQoL index score from the reported health state information. The UK value set has frequently been used in other Norwegian studies using the EQ-5D (34) and is recommended by the EuroQol group in the absence of country-specific value sets (34, 68, 80). Measures of HRQoL immediately after sustaining hip fracture were not collected due to the patients being admitted as emergencies and in most cases with a severely deteriorated health state. Instead all patients were given an equal EQ-5D-3L index score of 0.268, gathered from a systematic review of osteoporosis related utility values (81). This constant of 0.268 has been used in a previous study (34).

The pre-fracture EQ-5D-3L index score was unknown. In order to measure change in HRQoL from before fracture to 12 months post fracture, estimation of pre-fracture EQ-5D-3L index score are performed for all patients. An extensive literature search was conducted with the aim of finding a suitable method for estimating prefracture EQ-5D-3L index score.

Almost all identified studies of pre-injury assessment of HRQoL used retrospective assessments and asked patients to recall their pre-injury HRQoL (13, 15, 16, 71, 82-91). The recalled pre-injury scores consistently exceeded age- and sex-adjusted population normal, implying a systematic overestimation of the change in HRQOL from pre- to post-injury. Only two studies reported on prospective pre-injury assessment, based on prospective longitudinal cohort studies from a sample of initially non-injured patients (92, 93). Studies that did not have preference-based measures (PBM) of HRQoL available, estimated such data by mapping clinical measures, i.e the oxford hip score, or non-PBM of HRQoL, i.e., the SF-36, into the generic PBM of interest (EQ-5D index score). A mapping function is a prediction equation that is generated using the statistical relationship between a measure and a target PBM, estimated using regression analyses (94). Conceptual overlap between the two measures is an important consideration before mapping can be undertaken (95).

One of the identified studies showed that it is possible to reasonably predict the EQ-5D-3L index score from BI using regression methods (96). Thus, pre-fracture EQ-5D-3L index score for this master's thesis is estimated based on pre-fracture data on BI and a published mapping equation (see table 2).

Table 2 Published mapping equation to estimate EQ-5D-3L index score from BI data.

Overall EQ-5D-3L index score =	-0.113 + 0.020*Grooming + 0.126*Toilet + 0.011*Feeding + 0.051*Transfer + 0.039*Mobility + 0.092*Dressing + 0.040*Stairs + 0.026*bathing – 0.032*Bladder + 0.008*Bowels

Patients who died were assumed to have a linear decline in HRQoL from the last observed value until time of death (97), i.e., if a patient died at 6 months post-fracture, there was a linear decline from the observed HRQoL value at 4 months to the HRQoL value of zero at 6 months. The patient was then given the value of zero for the remaining time of follow-up.

Data on HRQoL is presented as mean (SD) EQ-5D-3L index score at each of the 5 measurement time points. Measures of change is presented as mean (95% CI) and percentage change from before fracture. Sub-analyses are performed to describe the estimated pre-fracture HRQoL for men/women in different age groups (<80, 80-90,>90) in order to compare the findings with other published results.

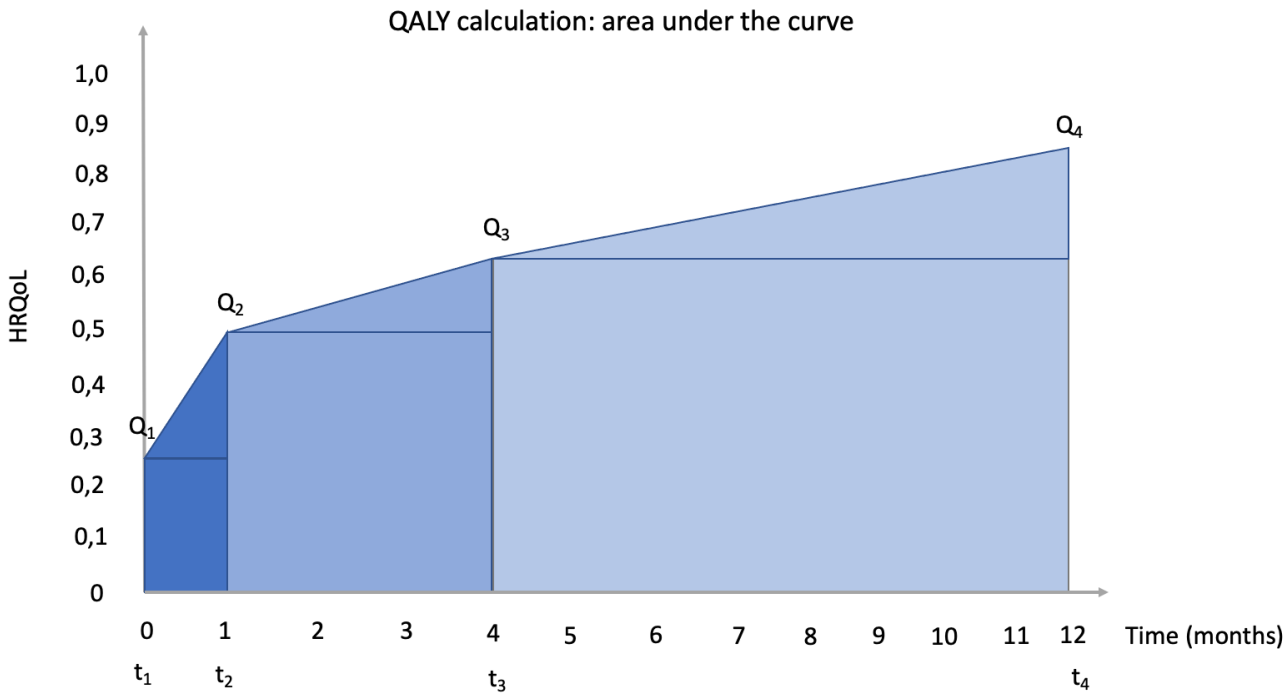
We calculated QALYs using the area under the curve (AUC) approach (See figure 5). This approach assumes a linear change in HRQoL over time. There is no guarantee that HRQoL would change in this manner, particularly with an acute state like a hip fracture. Several alternative patterns of deterioration and/or recovery would be possible.

In this thesis QALYs are calculated by the following:

$$\boldsymbol{QALY} = \sum_{\boldsymbol{t=0}}^{\boldsymbol{n-1}} \left[\frac{\boldsymbol{Q_t + Q_{t+1}}}{\boldsymbol{2}} \frac{\boldsymbol{T_{t+1} - T_t}}{\boldsymbol{T}} \right]$$

The numbers of measurements are 4 (at fracture, 1-, 4- and 12-months post-fracture), T is the time of the study period (12 months), and Q_t is the HRQoL index value at time t.

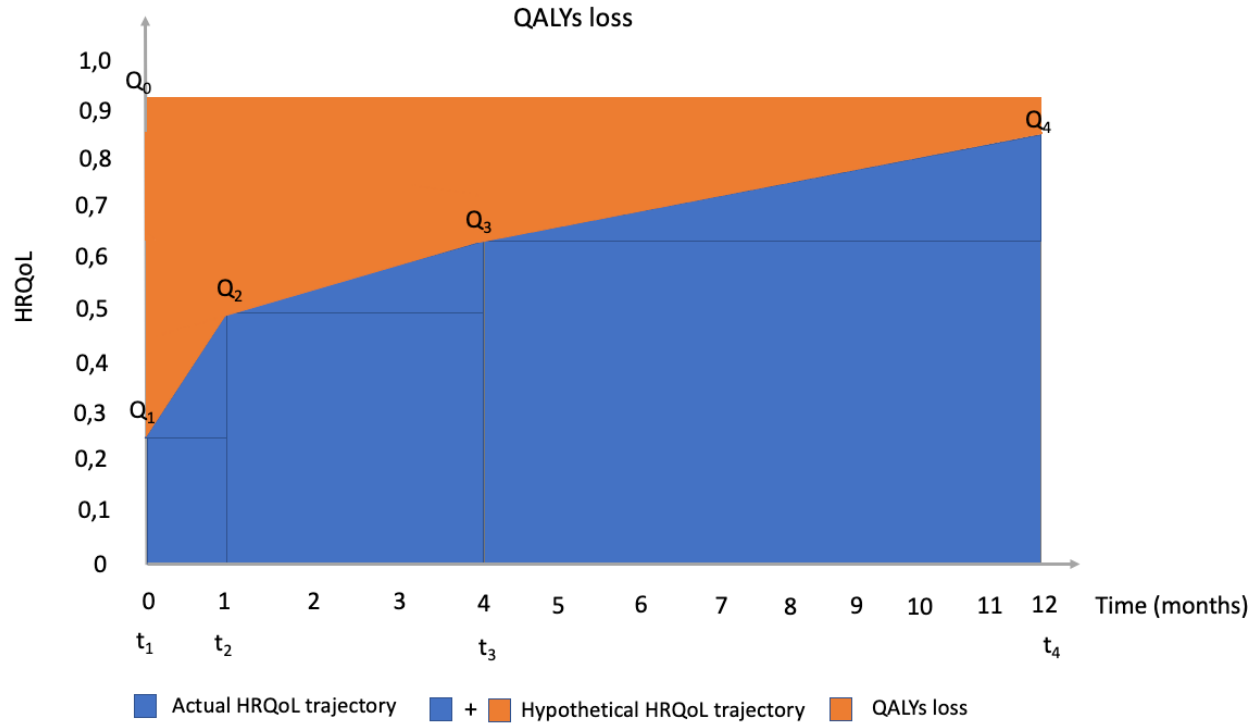
Figure 5. QALY calculation – area under the curve method.



In order to calculate QALYs loss a hypothetical trajectory was derived under the assumption that the patients´ HRQoL would have remained at the estimated pre-fracture level had the fracture not occurred. Accumulated QALYs loss was estimated as the difference between the areas under the curves of the hypothetical and actual QALY trajectories over the relevant time period (See figure 6). This was calculated according to the following formula:

$$\text{QALY loss} = Q_0 * 12/12 - \sum_{t=0}^{n-1}\left[\frac{Q_t + Q_{t+1}}{2}\frac{T_{t+1} - T_t}{T}\right]$$

Figure 6. The figure below provides a schematic description of the HRQoL index score trajectories after hip fracture, and QALY loss. The blue line (Q_1, Q_2, Q_3 and Q_4) represents the estimated actual HRQoL index score trajectory after fracture, derived using linear interpolation between observed HRQoL index score immediately after fracture and 1 month, 4 months, and 12 months post-fracture. The blue area represents the QALY for the first-year post fracture, calculated by AUC method. The orange line represents the hypothetical HRQoL trajectory in which patients were assumes to remail at their estimated pre-fracture HRQoL for the entire follow-up period of 12 months. The total-colored area (blue + orange) represents the hypothetical QALY for the first-year post fracture, calculated by AUC method. The orange area represents the difference between the hypothetical and actual QALY for the period, thus, the QALY loss.



Accumulated 12-months QALY loss is presented as mean (SD) and as a percentage change from before fracture. Sub-analyses are done to describe the QALY loss for different fracture types (intracapsular/extracapsular), age groups (< 80, 80-90, >90), and gender (men/women).

Instruments used for data collection

In addition to the instruments described below, EQ-5D-3L was used for the longitudinal assessment of HRQoL. This instrument is described in full in theoretical framework.

Barthel Index (BI)

BI is a measurement of p-ADL, and thus the level of independence (98). It is a 10-item questionnaire with a maximum score of 100. The 10 items on the BI are feeding (0-10 points), bathing (0-5 points), grooming (0-5 points), dressing (0-10 points), bowel control (0-10 points), bladder control (0-10 points), toilet use (0.10 points), transfer between bed and chair (0-15 points), mobility (0-15 points) and stair walking (0-10 points). Maximum score of each item is 5 to 15 points.

The BI is well established and widely used in clinical practice and research. It may be used both as a questionnaire or in interview (telephone or face to face) and still have acceptable precision (99). BI is found to have an acceptable sensitivity to change that is valuable in longitudinal studies, but is reported to have possible floor effect when used in very frail population and a possible ceiling effect when used in populations with better functional status (100).
Impairment in BI is a strong indicator of dependency and in many cases indicates need for 24-hour care (101)

Nottingham Extended Activities of Daily Living (NEADL)

NEADL is a measurement of i-ADD and was developed primarily for use in stroke patients (102), but has previously been used in hip fracture populations (34, 35).

It consists of four domains with 22 items scoring 0 to 3 (unable =0, with help =1, on my own with difficulty =2, on my own =3) points giving a maximal score of 66. *Mobility* with six items: outdoor walking, stair climbing, getting in- and out of a car, walking on uneven ground, ability to cross roads and use of public transport. *Kitchen activities* with five items: independent feeding, ability to make a hot drink, ability to transport a hot drink between two rooms, dishwashing and cocking a meal. *Domestics* with five items: managing own money,

hand washing of clothes, housework, shopping, and laundry. *Leisure time activities* with six items: Reading books or papers, use of telephone, writing letters, going out socially, gardening and driving.

When used in hip fracture populations, NEADL has shown less sensitive to change when used in healthier osteoarthritis patients (103) , and a ceiling effect has been observed in high functioning hip replacement patients (104).

Clinical dementia rating scale (CDR)

CDR is an established questionnaire-based method for evaluating cognitive function, and has been used to screen for dementia since 1982 (105). It consists of six domains: memory, orientation, judgment, community affairs, home and hobbies and personal care. Each item scores 0=normal, 0.5= slightly reduced, 1= mild cognitive failure, 2=moderate cognitive failure, and 3= severe cognitive failure. Further, the scores of each item are summarized into a total score which is used to categorize the patient into four categories: normal (0 points), possibly reduced (0.5 to 4 points), mild dementia (4.5 to 9.5 points), moderate dementia (10-15.5 points) and severe dementia (16 to 18 points) (106).

CDR allows for all sources of information to be used in scoring the patient even if it is primarily designed for careers and next of kin (107). It also allows for information to be collected retrospect (108).

Charlson comorbidity Index

Charlson comorbidity index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital records. It consists of 17 different diagnostic groups scoring from 1 to 6 points (109). Diagnosis of cardiac infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, pulmonary disease, connective tissue disease, peptic ulcer, liver disease and diabetes scores 1 point. Complicated diabetes, paraplegia, renal disease, and cancer scores 2 points. Metastatic cancer and severe liver disease scores 3 points and HIV-infection scores 6 points. A high score indicates a high level of comorbidities.

Statistical analyses

The IBM SPSS statistics program version 26 was used for all data analyses.
QQ-plots of residuals were visually inspected to assess the distribution of continuous variables. Data regarding categorical variables are generally presents using frequencies and proportions. For continuous variables, means, standard deviations (SD) and 95% confidence intervals (CI) are reported when relevant. Two-sided p values less than 0.05 will be considered statistically significant. Mean and SD are reported for all types of distributions as they are well defined and meaningful descriptive statistics for the purpose (110). The paired samples *t*-test, Mann Whitney U-test, Fisher's exact test, the One-Way Anova and the Kruskal-Wallis one-way Anova were used to evaluate any difference between groups or measures as appropriate.

In order to identify predictors of QALY loss a multivariate linear regression model were set up with QALY loss as the dependent variable and age (years), sex (male), type of fracture (extracapsular), living situation (living with others), comorbidity (Charlson comorbidity score), pre-fracture ADL-function (NEADL), pre-fracture HRQoL (estimated pre-fracture EQ-5D-3L index score), and pre-fracture cognitive status (CDR) as independent variables. Bivariate linear regression was performed for the dependent variable and each of the independent variables in order to assess the relationship between them and the strength of it. No p-value based cut-off was set to keep the independent variable in the multivariable regression model (111). The independent variables were chosen on anticipated assumptions derived from theory on the subject. Potential collinearity between variables was assessed with correlation coefficients. Complete case analysis was performed (n=354).

Handling of missing data in the master's thesis

Of the 387 patients included for the analysis in this master's thesis 59 died during the follow-up period of 12 months. These were given the score of zero from time of death (follows from the definition) (61, 65).

31 patients had missing values on the pre-fracture measurement of CDR. For the multivariable regression analysis, complete case analysis was performed. Sensitivity analyses were done to identify possible differences between those with missing and those with

complete data considering age, pre-fracture HRQoL, pre-fracture ADL, comorbidity and QALY loss.

Ethical approval

All patients involved have given their written informed consent for participation. Next-of-kin provided a preliminary consent for patients deemed not to give consent at inclusion. Repeated information about the trial was provided at each follow-up. THFT was approved by the Regional Committee of Ethics in Medical Research (Mid-Norway) (REK4.2008.335), The Norwegian Social Science Data Services (NSD19109), and the Norwegian Directorate of Health (08/5814).

Results

Patient characteristics and pre-fracture function

Baseline characteristics and pre-fracture function of the patients are shown in table 3. Of 397 possible, 387 patients were included in the analysis. 8 patients died before registration of prefracture BI, and two persons withdrew from further follow-up and were excluded due to no follow-up data on EQ-5D-3L.

Table 3 Characteristics and pre-fracture function of participants. N = 387

	Mean (SD)	
Age (years)	83.2 (6.1)	
Barthel Index (0-100)	90.9 (12.7)	
Nottingham Extended I-ADL (0-66)	42.2 (17.6)	
Clinical Dementia Rating Scale (0-18) [a)]	2.7 (2.1)	
Charlson Comorbidity Index (1-6)	2.27 (2.1)	
	n and % [b)]	
Sex		
Female	291/387	75.2%
Male	96/387	24.8%
Type of fracture		
Intracapsular	240/387	62%
Extracapsular	147/387	38%
Cohabitation status		
Living alone	230/385	59.4%

[a)] Clinical Dementia Rating Scale was missing for 31 participants
[b)] Number of participants with complete data varied between tests and are reported in proportion of those with complete data

Estimated pre-fracture HRQoL

The overall mean pre-fracture HRQoL was estimated at 0.64 (SD 0.10).
The mean and median estimated pre-fracture HRQoL for men and women in different age groups are presented in table 4. There is no difference in estimated pre-fracture HRQoL between men and women according to the Mann Whitney U-test (p-value = 0.83). Estimated pre-fracture HRQoL declined with increasing age for both men and women. This difference between age-groups was statistically significant according to the Kruskal-Wallis Test (p-value = 0.00).

Table 4 Mean and median estimated pre-fracture HRQoL (EQ-5D-3L index score) by gender- and age groups.

Sex	Age	N	Mean (SD)	Median (min, max)
Men	<80	26	0.65 (0.11)	0.69 (0.19, 0.69)
	80-90	55	0.64 (0.10)	0.69 (0.28, 0.73)
	>90	15	0.64 (0.07)	0.68 (0.49, 0.73)
	Total	**96**	**0.64 (0.10)**	**0.69** (0.19, 0.73)
Women	<80	88	0.65 (0.12)	0.69 (0.08, 0.73)
	80-90	154	0.65 (0.08)	0.69 (0.26, 0.73)
	>90	49	0.61(0.10)	0.63 (0.21, 0.70)
	Total	**291**	**0.64 (0.10)**	**0.69** (0.08, 0.73)
Total	<80	114	0.65 (0.12)	0.69 (0.08, 0.73)
	80-90	209	0.65 (0.08)	0.69 (0.26, 0.73)
	>90	64	0.62 (0.09)	0.65 (0.21, 0.73)
	Total	**387**	**0.64 (0.10)**	**0.69** (0.08, 0.73)

Distribution of the estimated pre-fracture HRQoL

The distribution of the estimated pre-fracture HRQoL (EQ-5D-3L index score) is shown in figures 6 and 7. A seen from the histogram the distribution is skewed to the left and unimodal with a peak around 0.70. The negatively skewed distribution is also clearly shown in the boxplots where the median is close to the third quartile. The range is 0.65, with the lowest value at 0.8 and the highest at 0.73. Nonnormality is confirmed by skewness (-2.6) and kurtosis tests (8.2). As seen from the boxplots, there are multiple outliers and extreme values below the first quartile. Though possible, there are no negative values.

Figure 6 Histogram: Distribution of estimated pre-fracture HRQoL (EQ-5D-3L index score) in 387 hip fracture patients. Possible values -0.594 to 1.

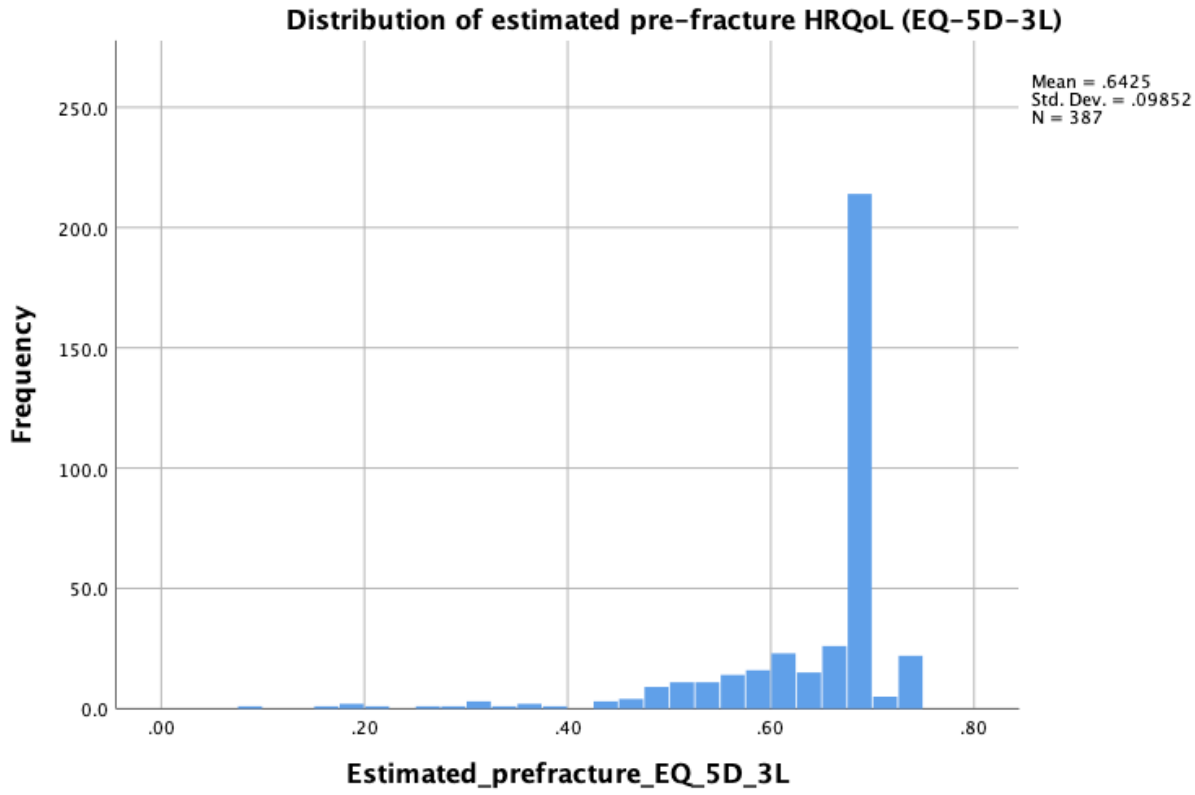
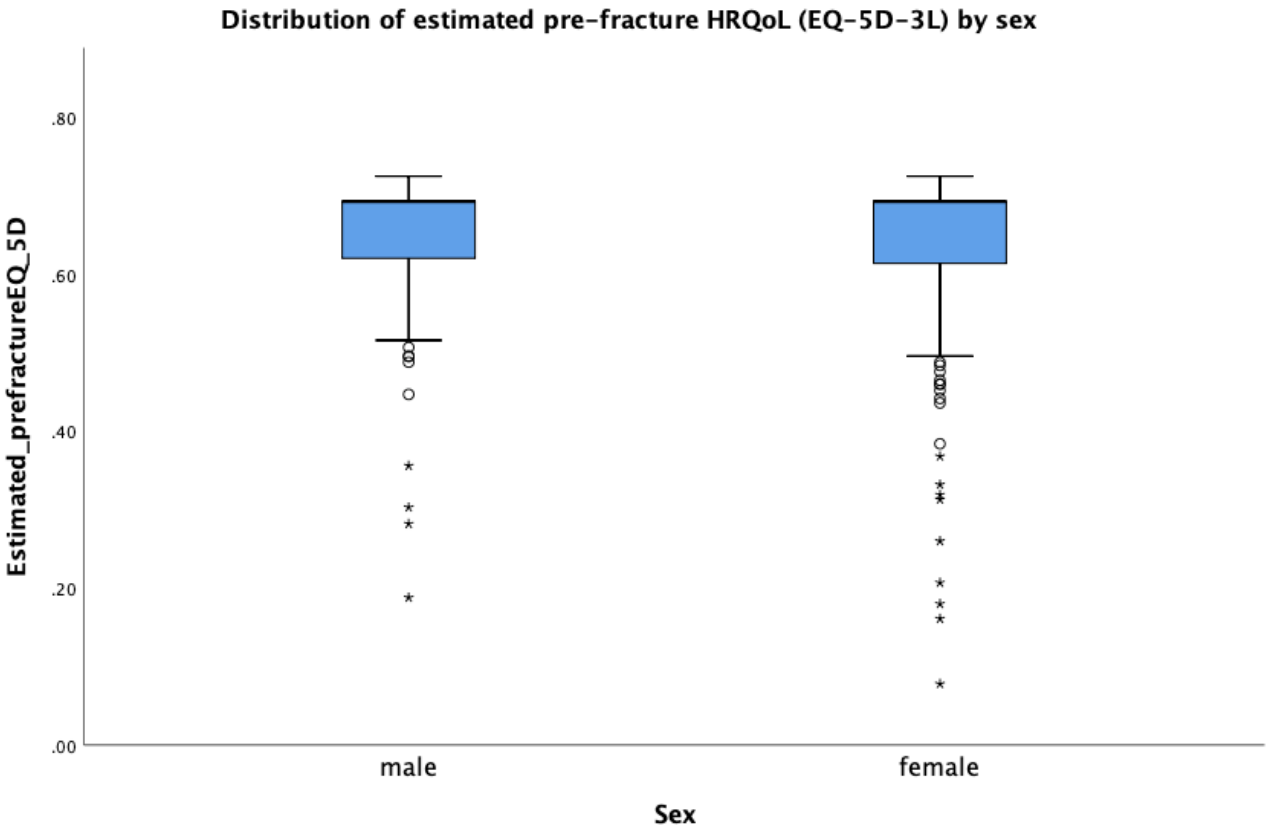


Figure 7 Boxplot: Distribution of estimated pre-fracture HRQoL (EQ-5D-3L index score) by sex.



Change in HRQoL

Mean HRQoL (EQ-5D-3L index score) at each time point and % change from before fracture is presented in table 5. Men exhibited a lower mean HRQoL than women at 4 and 12 months, but this difference was not significant according to a Mann-Whitney U Test. There was a significant difference in HRQoL before fracture and 12-months post fracture (0.12, 95% CI 0.08 to 0.15). This difference is both clinically and statistically significant according to the Wilcoxon Signed Rank Test (p-value =0.00). The change in HRQoL from before fracture to 12-months post fracture is visualized in figure 8.

Table 5 Change in mean HRQoL (EQ-5D-3L index score) for men and women 12 months following hip fracture.

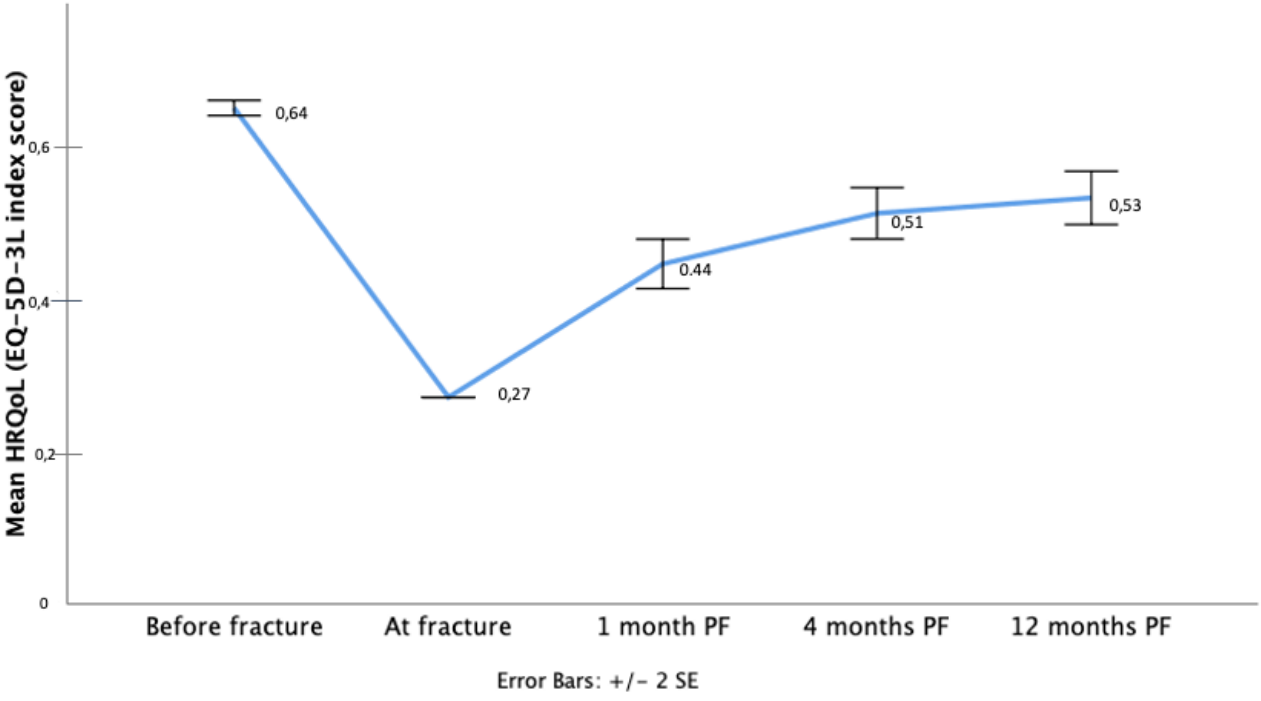
	Mean EQ-5D-3L index score (95% CI), % change from before fracture				
	Pre-fracture[a)]	At fracture[b)]	1 month PF	4 months PF	12 months PF
Women (n=291)	0.64 (0.63 to 0.65)	0.27	0.44 (0.40 to 0.48)	0.52 (0.48 to 0.56)	0.54 (0.50 to 0.58)
Men (n=96)	0.64 (0.62 to 0.66)	0.27	0.45 (0.38 to 0.51)	0.46 (0.39 to 0.53)	0.48 (0.51 to 0.58)
p-value	0.83		0.96	0.17	0.26
Total (n=387)	**0.64 (0.63 to 0.65)**	**0.27**	**0.44 (0.41 to 0.47)**	**0.51 (0.47 to 0.54)**	**0.53 (0.49 to 0.56)**
		-42.2%	-31.3 %	-20.3%	-17.2%

PF post fracture

a) Estimated from pre-fracture BI data

b) Constant derived from a systematic review

Figure 8 Line chart: Change in mean HRQoL (EQ-5D-3L index score) over the 12-month follow-up period.



Mortality

The number of patients who died during the 12 months follow-up period is presented in table 6. The total of 59 mortalities corresponds to a one-year mortality of 15.2 %. A crosstabulation showed that 28.1 % of male patients and 11 % of female patients were dead at 12 months post fracture. This difference in mortality between genders was statistically significant according to the Fisher´s exact test (p-value =0.00)

Table 6 Mortality in the 12-months post fracture period

Time period	Frequency	Accumulated percent
0–1 month PF	16	4.1 %
2-4 months PF	17	8.5 %
5-12 months PF	26	15.2 %
Total	**59**	**15.2 %**

PF post fracture

QALY loss

The mean 12-months loss in QALY was 0.15 (95% CI 0.13 to 0.18) (see table 7). This represents a 23.4% loss in QALYs the first-year post fracture. The QALY loss is visualized in figure 9. Subgroup-analysis for gender, age groups and fracture type are shown in table 8. Men in the age group >90 with an extracapsular hip fracture exhibited the greatest QALY loss. The difference between genders, age groups and fracture types were non-significant.

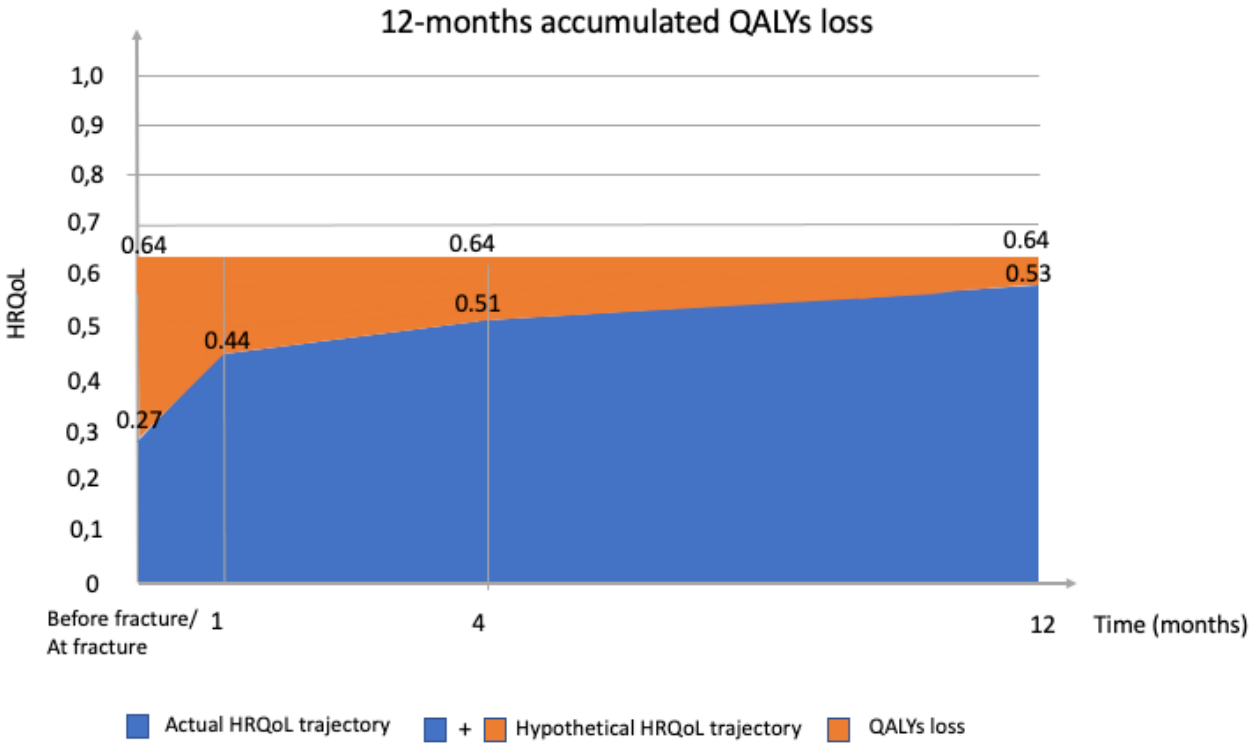
Table 7 Subgroups analysis of QALY loss

		12 months QALY loss	
	n	Mean (95% CI)	p-value
Total		**0.15 (0.13 to 0.18)**	
Sex			0.15*
Male	96	0.19 (0.13 to 0.24)	
Female	291	0.14 (0.11 to 0.17)	
Age group (years)			0.18**
<80	114	0.15 (0.10 to 0.19)	
80-90	209	0.14 (0.10 to 0.17)	
>90	64	0.21 (0.13 to 0.18)	
Fracture type			0.19*
Intracapsular	240	0.14 (0.10 to 0.17)	
Extracapsular	147	0.17 (0.14 to 0.21)	

*Independent samples t-test

**One-way Anova test

Figure 9 Area chart of the mean 12-months accumulated QALY loss. The orange area visualizes the difference between the hypothetical and actual HRQoL trajectory over the 12-month period, and thus, the QALY loss.



Multivariate regression analysis and factors associated with QALY loss

The bivariate analyses showed that pre-fracture cognitive status (CDR), pre-fracture ADL-functioning (NEADL) and comorbidity status at time of fracture (Charlson Index) were associated with QALY loss. Results from the multivariate regression model is shown in table 8. The model was run to predict QALY loss from sex, age, fracture type, pre-fracture HRQoL, pre-fracture ADL, pre-fracture CDR, living situation and comorbidity status. These variables statistically significantly predicted QALYs loss, F (8, 345) = 7.29, p <0.001, R^2=0.15. I.e the equation demonstrated that 15% of the variation in QALY loss at 12 months was explained by the model.

Table 8 Multivariable regression analysis summary for predicting QALYs loss

Variable	B	95% CI	β	t	p
(Constant)	0.213	(-0.222 to 0.648)		0.962	0.337
Male[a)]	-0.033	(-0.096 to 0.029)	-0.54	-1.041	0.290
Age	-0.001	(-0.006 to 0.004)	-0.23	-0.428	0.669
Extracapsular fracture[b)]	-0.034	(-0.088 to 0.019)	-0.63	-1.272	0.204
Pre-fracture HRQoL	0.447	(0.089 to 0.804)	0.164	2.458	**0.014**
Living with others[c)]	0.029	(-0.027 to 0.085)	0.054	1.014	0.311
Pre-fracture NEADL	-0.006	(-0.009 to -0.004)	-0.418	-5.280	**0.000**
Pre-fracture CDR	-0.005	(-0.013 to 0.004)	-0.069	-1.075	0.283
Charlson Comorbidity Score	0.020	(0.007 to 0.032)	0.163	2.096	**0.002**

Note: R^2 = 0.15 CI = confidence interval for B

Bold indicates significance at 95%

[a,b,c)] Control groups are female, intracapsular fracture and living alone respectively.

From the multivariate regression analysis, we found that pre-fracture ADL, pre-fracture HRQoL and comorbidity present at time of fracture was significant predictors of QALY loss. The model predicted that those with a high pre-fracture HRQoL, high comorbidity and low pre-fracture ADL-functioning experience a greater QALY loss at 12 months post fracture.

Complete case

31 patients had missing values on the pre-fracture measurement of CDR. For the multivariable regression analysis, complete case analysis was done. According to an independent samples t-test, there were no statistically significant differences between the patients with or without missing values on CDR when it comes to age (p-value =0.40), pre-fracture HRQoL (p-value =0.67), pre-fracture ADL (p-value = 0.81), comorbidity (p-value =0.70) and QALYs loss (p-value =0.84).

Discussion

In this longitudinal cohort study, we aimed to quantify the change in patient reported HRQoL the first year after sustaining a hip fracture in a cohort of elderly patients in Trondheim, Norway. A secondary objective was to investigate which pre-fracture characteristics and factors are associated with the change in HRQoL the first 12 months post fracture.

To the best of our knowledge, this is the first study to quantify the change in HRQoL following hip fracture in a sample of Norwegian elders. We found that a hip fracture had a substantial negative impact on the patients HRQoL, and that the patients did not recover their pre-fracture levels. In terms of QALYs, we estimated a mean QALY loss of 0.15 the first year following hip fracture. This loss is equivalent to an average loss of 55 days in full health for each of the patients experiencing a hip fracture.

Even prior to sustaining the fracture, the patients in this study showed a deteriorated HRQoL with a mean prefracture HRQoL index score of 0.64 (SD 0.10). This is seen in correspondence to most older hip fracture patients being frail, having pre-existing comorbidities and showing a functional deterioration that is typical for geriatric patients (50). In comparison, this is evidently lower than pre-fracture HRQoL found in a Swedish hip fracture population (0.80), and also lower than the pooled estimate (0.76) derived from a systematic review and meta-analysis of published literature (81). This may reflect differences in inclusion criteria and pre-fracture characteristics such as age, cognitive- and comorbidity status. Noteworthy, the Norwegian population norms is estimated at a mean of 0.79 in this age group (112). If the estimation of pre-fracture HRQoL in this study somehow is biased, and is in reality higher, this would give a conservative estimate of QALY loss.

The occurrence of a hip fracture was associated with a substantial drop in HRQoL. The mean HRQoL index score at the immediate post-fracture period was set to 0.27. This equals a 42.2 % change from before fracture. As expected, HRQoL improved with time from the fracture event. At 1-, 4- and 12-months post-fracture, HRQoL improved to 0.44, 0.51and 0.53 respectively. However, at 12 months post fracture HRQoL had not fully return to the pre-fracture baseline level. This pattern, with a very marked drop in immediately post-fracture period and partial recovery, is consistent with the reports from other studies with follow-up of at least 12 months (42, 52). The mean change in HRQoL from before fracture to 12-months

post fracture was 0.12 and was both clinically and statistically significant, meaning that the occurrence of a hip fracture has an evident impact on these elderly patient´s HRQoL.

According to the sub-group analysis, estimated pre-fracture HRQoL declined with increasing age, and the patients over 90 years of age experienced the lowest pre-fracture HRQoL. This is concordance with other studies, showing that HRQoL is negatively associated with higher age (113). There was no difference between men and women in pre-fracture HRQoL, but men trended towards a lower HRQoL than women at both 4 (0.46 vs. 0.52, p-value = 0.17) and 12 (0.48 vs. 0.54, p-value = 0.26) months post fracture. Further, subgroup-analysis showed that men exhibited a slightly higher but not statistically significant mean QALY loss than women (0.19 vs. 0.14, p-value = 0.15). This should be taken with some caution since only 25 % of the sample was male and because this variable was not statistically significant, neither in direct comparison nor in the multivariable regression analysis. The oldest patients (>90) had a greater mean QALYs loss that the younger age-groups, but this difference was non-statistically significant, nor was the difference in QALYs loss between fracture types (intra- vs. extracapsular fracture).

We found a 1-year mortality of 15.2 %. This is lower than findings in other hip-fracture studies, where 1-year mortality was estimated between 24-30% (40-42). The exclusion of elders institutionalized prior to the hip fracture are likely to account for the low mortality in this cohort. Further, exclusion of these institutionalized hip fracture patients is likely to bias the recovery rate of HRQoL and thus, QALY loss. The significantly higher mortality among men than women is in concordance with findings of other studies (114). Further, QALY loss in survivors (n=328) was 0.09. This means that mortality, premature death as a consequence of the hip fracture, accounts for 40 % of the QALY loss in this population. QALY loss were higher in men than women (0.19 vs. 0.14), and this difference was mainly attributed to high mortality in men. Given the increasing number of patients with comorbidity due to advanced age and the high mortality among hip fracture patients, optimizing the preoperative and postoperative care of patients with comorbidities, as well as focusing on complications known to be related to these conditions, could potentially reduce mortality, and thus, QALY loss.

From the multivariate regression model, we identified three prefracture factors that were statistically significant predictors of QALY loss from before fracture to 12 months post-fracture. These were pre-fracture HRQoL index score, pre-fracture NEADL and Charlson comorbidity score present at time of fracture. The finding of pre-fracture HRQoL index value as a significant predictor of QALYs loss over the first-year post fracture is in concordance with other studies (13, 16, 17). To our knowledge, no other studies have investigated the impact of pre-fracture ADL-functioning and present comorbidity on QALY loss. These findings have some implications for clinical practice and suggest that early identification of pre-fracture vulnerability in terms of lower ADL- functioning and present comorbidities in patients with hip fracture is important for prognostic counselling, care planning, and tailoring of treatment. By targeting these patients at an early stage one can conceivable prevent QALY loss in some extent. The multivariable regression model explained 15 % of the variation of loss in QALY the first-year post-fracture. This indicates that there are other factors or variables, other than those we have examined, that explain the majority of the variance. This topic warrants further investigation.

The mean loss of 0.15 QALY is equivalent to an average loss of 55 days in full health for each of the patients experiencing a hip fracture. This represents a substantial health impact, both on the individual level and for the society. And the total burden is increasing. A recent study estimated that the future burden hip fractures in Norway is likely to double from 2020 to 2040 due to population growth, even if the fracture rate continues to decline (6). In this study, we estimated QALY loss the first year after hip fracture. It is important to point out, that for patients experiencing hip fractures, the loss will most likely last for the remaining lifespan.

When assessing severity, absolute shortfall, will in many cases be lesser for diseases affecting older age groups. This implies that diseases depriving patients of many future QALYs will be assessed as more severe than diseases depriving patients of fewer future QALYs. Age is not in itself a priority criterion in Norway. However, age will necessarily be of importance when absolute shortfall is used as a measure of severity. In short, the average age at onset of the disease, and how much HRQoL and longevity can be lost, are the two most important factors (115). A disease that occurs late in life will to a lesser extent reduce the potential for future QALY loss. The mean age for the hip fracture patients in this study was 83.2. In comparison, life expectancy of the Norwegian population is 84.9 for women and 81.5 for men (116). This

implies that this patient group has a lesser potential for loss of QALYs, and thus, will be assessed as less severe compared to diseases that occurs in a younger patient population. It is stressed that this is not an indication of a deprioritization of elderly patients, and that, on the clinical level, the elderly who need medical assistance and care will continue to receive it.

Further, the estimate of QALY loss depends crucially upon the data sources, methodologies used, and weights given to different health states, and this need to be taken into consideration when assessing the results provided. E.g., if we were to use population-based norms of HRQoL index score as a proxy for HRQoL before fracture this would have resulted in a mean QALY loss of 0.30 (113). This would be an overestimation of QALY loss and does not account for the fact that this population of hip fracture patients already before fracture is a frailer population with more comorbidities present than their peers (12). In contrast, excluding patients who died during the 12-months of follow-up gives an estimated mean QALY loss of 0.09. Excluding patients who die before the endpoint of a study is usually not problematic as long as the number is not too high. For this population, however, mortality rate is high, which leads to missing data and consequently lost precision in terms of estimating outcomes. Excluding patients who die during follow-up leads to underestimation of the QALY loss and thus the burden of hip fracture. In our study, patients who died during follow-up were not excluded, but instead given the EQ-5D-3L index score of zero for the remaining time of the study. This use of death-adjusted estimates is in concordance with recommendations for reporting HRQoL in this population (97).

Prospective derived data on HRQoL should be used whenever possible. But with an acute event like a hip fracture, collecting prospectively data on pre-fracture HRQoL, is difficult, if not impossible. Studies using retrospective recalled pre-injury values, shows a widely varying timings of assessment, from soon after injury up to two years after. Further, the recalled pre-injury HRQoL scores consistently exceeds age- and sex-adjusted population norms, which suggests recall bias (14, 71, 78, 81, 117, 118). Due to comorbidity, elders experiencing hip-fracture have showed significantly poorer overall health and functional ability pre-fracture than the general population of same age and sex (12). Using recall implies an overestimating in pre-fracture HRQoL, and thus, an overestimated loss of QALYs. This calls for new thinking about ways of estimating pre-fracture HRQoL index scores. This study thus contributes to the research basis for mapping of HRQoL data and shows that mapping from BI

is a suitable way of estimating pre-fracture HRQoL whenever prospective data on HRQoL is not collected.

The predictive model chosen to estimate pre-fracture HRQoL index score had moderate R^2 statistics (96), and the lack of overlap between BI and EQ-5D-3L in some dimensions (i.e anxiety/depression and pain/discomfort) may contribute to this. However, the predictive model showed to perform consistently across the validation datasets and the goodness-of-fit statistics showed that the model was robust and did not suffer from any misspecification errors. Nevertheless, mapping should always be considered second best to direct and prospective EQ-5D-3L measurement since it introduces additional errors and assumptions. Thus, the lack of direct prospective EQ-5D-3L measurement before fracture is a major limitation of this study and may cause prediction bias. At present, there is relatively little evidence on the extent to which mapping algorithms developed in one population generalize to another (119).The performance of other clinical measures or non-PBM on mapping pre-fracture HRQoL index scores, and their generalizability, should be investigated in further research.

The estimated pre-fracture HRQoL index value in our study displayed a wide range of values, from 0.08 to 0.73. This may be explained by the fact that hip fracture patients represent a heterogeneous population, ranging from the relatively robust to frail elders with deteriorated health state. There are multiple lower outliers, but no values above 0.73, thus, no higher outliers. A study reporting on data from the Norwegian hip fracture register (n =10375) found that the majority of patients reported on no problems before fracture in all five dimensions of the EQ-5D-3L, which yields an index score of 1 (9). Thus, it seems unlikely that none of the 387 patients in this study did not score better than 0.73. This may be a major limitation of the method chosen for estimating the pre-fracture HRQoL index score in this study. Studies have found that mapping functions predict values less extreme than the values which they are used to map into (120, 121), suggesting the issue of prediction bias. Others have pointed out that any regression-based mapping model would predict less extreme values because of the phenomenon of regression to the mean (122). To the best of our knowledge, the mapping function chosen in this study has not been investigated or used in clinical setting before, thus, there is a lack of basis for comparison.

In our study, QALY loss was calculated under the assumption that patients would have remained at their pre-fracture HRQoL the whole 12-months period had the hip fracture not occurred. One pressing problem in estimating QALYs loss for hip fracture patients is knowledge about the counterfactual HRQoL. In this old and frail population, where comorbidities are present, it is reasonable to believe that HRQoL would have deteriorated to some extent due to natural life course irrespective of the fracture (113). Thus, this study gives an overestimation of QALY loss.

The prevalence of cognitive impairment (CI) among elderly with hip fractures is estimated as high as 37 % (123). According to a recent Norwegian study, hip fracture patients with CI have lower HRQoL than those without CI both before and after the hip fracture (22). The study concluded that CI has a negative impact on HRQoL after a hip fracture, and that patients with CI experience a greater decline in HRQoL than for those without CI. Patients with CI are often excluded from studies because of the difficulty in obtaining informed consent from patients or proxies. Excluding these patients can lead to systematic bias in studies of hip fracture patients. By including patients with CI, our study gives a more accurate estimate of QALY loss in this population.

387 hip fracture patients were included for the analysis in this study. The mean age was 83.2, and 72 % were women. This is in concordance with a large Norwegian study of hip fracture patients (n=34.675) based on data from the Norwegian Hip Fracture Register, where mean age was 82 and 74% were women (22). In concordance with other studies, we found a moderately impaired ability to perform activities of daily living before fracture, and that this impairment was greater in I-ADL (NEADL) than P-ADL (BI) (124, 125). As expected in this population, comorbidity and cognitive impairment was to some extent present. In relative terms, comorbidity was present in some extent for 80.4 % of the patients. Other studies have reported on lower frequencies of pre-fracture comorbid conditions, ranging from 45-60% (114, 126, 127). This indicates that our selection of patients is representative for the Norwegian hip fracture population. Further, the inclusion of cognitive impaired patients in this study may reflect on this higher presence of comorbidity.

Conclusion

A hip fracture has a dramatic impact on the patients´ HRQoL, and the deterioration in HRQoL sustained also one year after the fracture occurred. The estimated pre-fracture HRQoL index value of 0.64 shows that it is reasonable to map pre-fracture HRQoL data whenever not collected. The mean QALY loss of 0.15 represents a substantial impact on these patients in terms of poor HRQoL and premature mortality. Pre-fracture HRQoL, pre-fracture ADL-functioning and present comorbidity at time of fracture were predictors of the QALY loss. Our findings emphasize the importance of preventing hip fracture and optimizing both pre- and postoperative care for this vulnerable and frail population of elders in order to prevent morbidity and mortality, and thus, loss of QALYs. Further, failure to fully account for the impact of hip fractures on QALYs could result in hip fracture interventions being undervalued in priority setting.

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