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

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Abstract

Objective: 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 one 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.

Design: Prospective observational follow-up cohort study.

Setting: Secondary care. Ten participating centres in Brabant, the Netherlands.

Participants: 1091 patients entered the study and 696 patients completed the study. Patients with a hip fracture aged 65 years and older or proxy respondents for patients with cognitive impairment were included in this study.

Main outcome measures: The primary outcomes were HS (EuroQol-5 Dimensions questionnaire; EQ-5D) and capability wellbeing (ICEpop CAPability measure for Older People; ICECAP-O). Pre-fracture frailty was defined with the Groningen Frailty Indicator (GFI), with GFI ≥4 indicating frailty. Participants were followed up at one month, three months, six months and one year after hospital admission.

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

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

Strengths and limitations of this study:

- This study addresses the paucity of knowledge of frailty in elderly patients with a hip fracture
- This multicenter prospective cohort study included a large number of participants and proxy participants in different geographic locations, which increases the generalizability of this study.
- 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.
- This results from this study shows that pre-fracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

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 pre-fracture, 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 one 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.

Materials 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 one week and one, three, six and twelve 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 one 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 pre-fracture information (T0) was gathered one week or one month after hip fracture by self- or proxy-reported questionnaires. The following data were collected at baseline within one 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 one week (T1), one month (T2), three months (T3), six months (T4) and one 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 (supplementary file). 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[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 generic health utility instrument, is used to measure 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[19]. The EQ-5D has good measurement properties and could be used to measure outcomes for patients recovering from hip fracture[11]. The dimensions of the EQ-5D were dichotomized in this study, with 0 indicating no problems and 1 indicating moderate and severe problems.

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[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]. 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 one 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 (pre-fracture 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 pre-fracture 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.

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)
Pre-fracture living in institution (N,%)	151 (21.7)	140 (37.7)	11 (3.4)
Pre-fracture 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 pre-fracture 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). Pre-fracture frailty was associated with pre-fracture HS, adjusted for residential status as a confounder (β-0.29; SE 0.02; $p<0.001$; 95% CI -0.33, -0.26). 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 pre-fracture, 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, 1.734) experienced by frail patients over one year, compared with the problems in the non-frail group.

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

	Crude			Adjusted[a]		
EQ-5 Domain	**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 pre-fracture status of the EQ-5D domain, age, pre-fracture 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, -0.299) and self-rated health (β -21.9; 95% CI -24.2, -19.6) in elderly patients one 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, -0.069) for the association between frailty and health status, adjusted for deceased drop-outs and for confounders, including pre-fracture EQ-5D score, age, pre-fracture residential status, pre-fracture 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 pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia

[b] Adjusted for death

[c] Adjusted for death, and pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and

dementia

Abbreviations: EQ-5D: Euroqol 5 dimensions; EQ-VAS Euroqol Visual Analogue Scale; ICECAP-O: ICEpop CAPability measure for Older People; **β**: Regression coefficient; CI: confidence interval

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226 *The longitudinal association between frailty and capability wellbeing*

227 Figure 4 shows differences in capability wellbeing between frail and non-frail patients during all

228 follow-up time points ($p<0.0001$). We found a significantly strong negative association on average

229 between frailty and capability wellbeing over time, with a death-adjusted regression coefficient that

230 included all confounders of β -0.146 (95% CI -0.187, -0.106; Table 3).

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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 one year after hip fracture. Confounders, such as pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia, weakened the association between frailty and QoL, but the association remained significant and clinically relevant. Our findings demonstrate that pre-fracture 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 our study, HS and capability wellbeing do not improve substantially within six 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]. 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[32].

It is remarkable that in the non-frail group, a high percentage of individuals do not return to pre-fracture 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[33]. 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 pre-fracture frailty status and HS data were only collected in patients who flowed into the study until one 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 pre-fracture capability wellbeing. Second, frail patients showed a higher capability wellbeing score at one-week follow-up than at one-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. 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 one 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[34]. 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. 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 pre-fracture 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 one year after hip fracture, even after adjusting for pre-fracture HS, age, pre-fracture residential status, pre-fracture 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 pre-fracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

Contribution of authors:

CR, NK, LM, TG and MJ contributed to conception and design of this study. CR, ML, NK and LM contributed to the data collection. CR, ML, NK, LM and MJ contributed to the analyses and interpretation. CR, ML, NK, LM, JS, TG and MJ contributed to preparation of the manuscript. The final version of the article was approved by all the authors.

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Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

Figure 2. Patterns of health status according to frailty status over time.

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

Figure 4. Patterns of capability wellbeing according to frailty status over time.

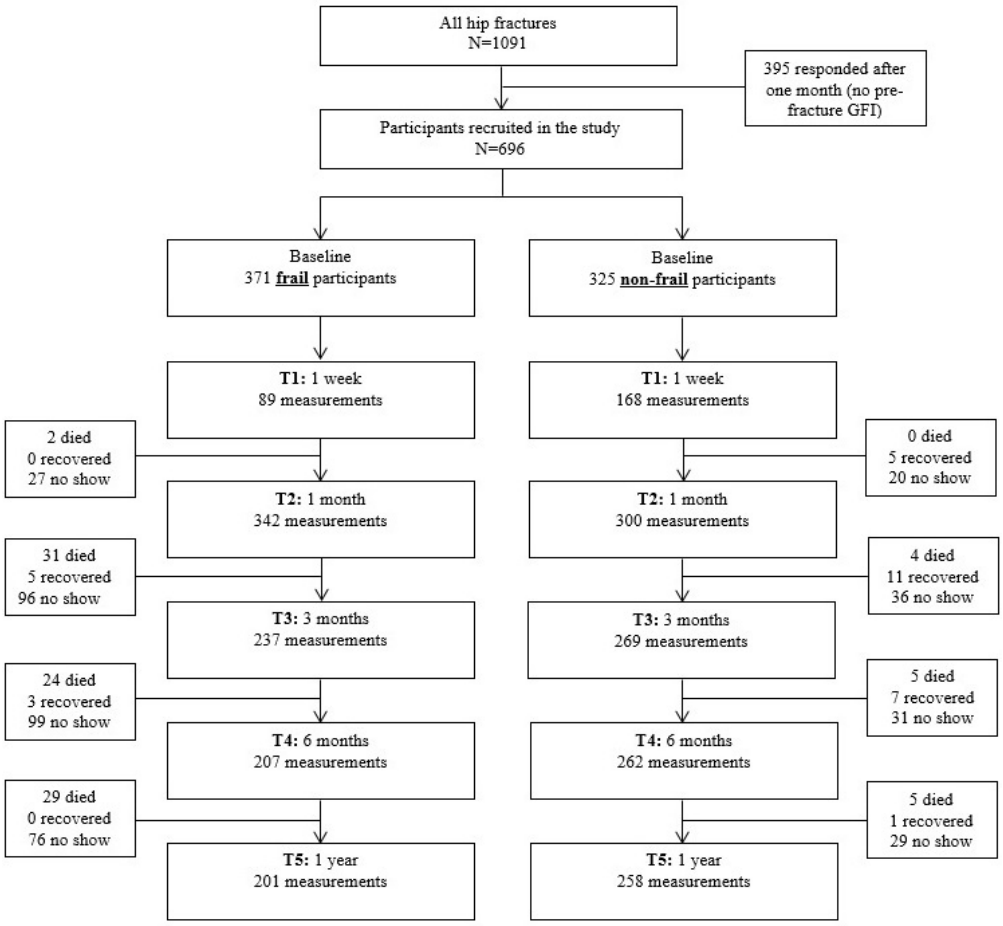

Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

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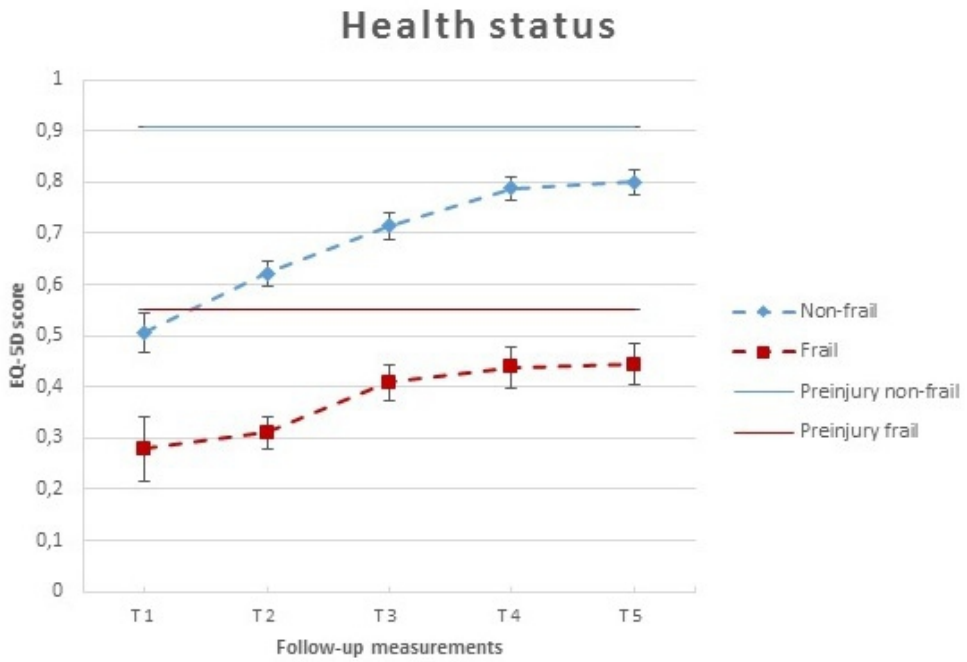

Figure 2. Patterns of health status according to frailty status over time.

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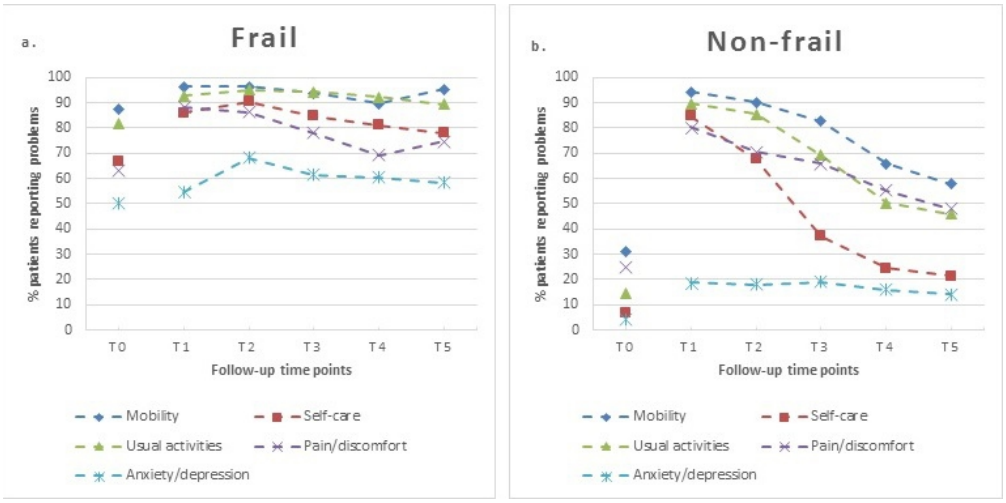

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64x32mm (300 x 300 DPI)

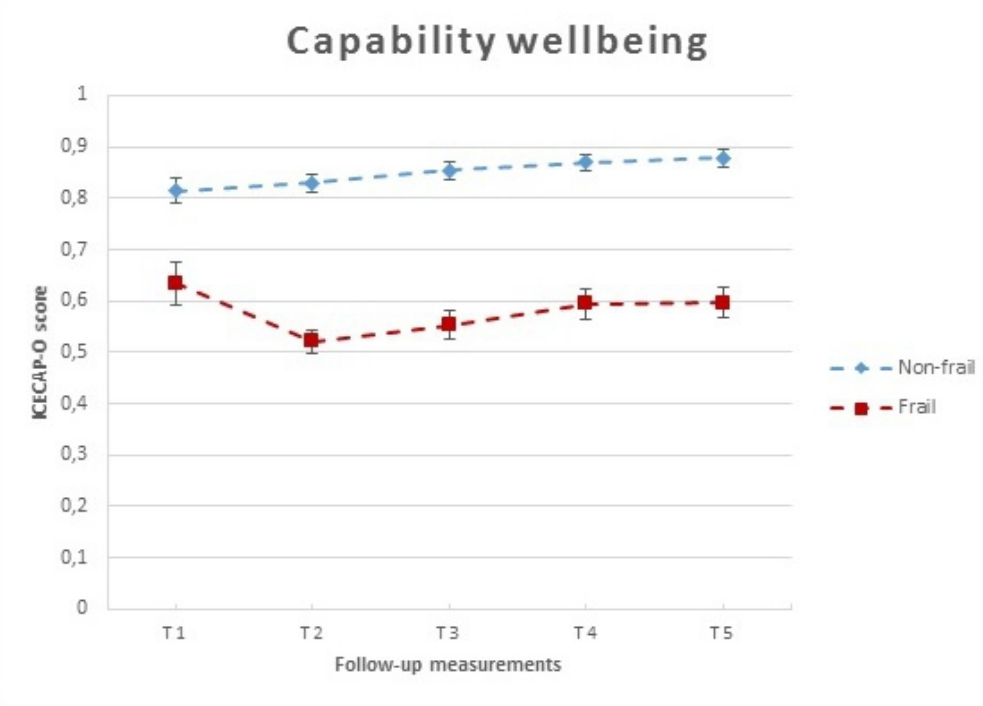

Figure 4. Patterns of capability wellbeing according to frailty status over time.

47x33mm (300 x 300 DPI)

APPENDIX 1: 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

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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

Word count: 3253

Abstract

Objective: 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 one 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.

Design: Prospective observational follow-up cohort study.

Setting: Secondary care. Ten participating centres in Brabant, the Netherlands.

Participants: 1091 patients entered the study and 696 patients completed the study. Patients with a hip fracture aged 65 years and older or proxy respondents for patients with cognitive impairment were included in this study.

Main outcome measures: The primary outcomes were HS (EuroQol-5 Dimensions questionnaire; EQ-5D) and capability wellbeing (ICEpop CAPability measure for Older People; ICECAP-O). Pre-fracture frailty was defined with the Groningen Frailty Indicator (GFI), with GFI ≥4 indicating frailty. Participants were followed up at one month, three months, six months and one year after hospital admission.

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

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

Strengths and limitations of this study:

- This study addresses the paucity of knowledge of frailty in elderly patients with a hip fracture
- This is multicenter prospective cohort study included a large number of subjects
- Patients and proxy participants were included in different geographic locations, which increases the generalizability of this study.
- Participants may not accurately recall their health status prior to the fracture, which might affect the results.
- The frail group contained more no-show cases, which could resulted in selective drop-out.

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 pre-fracture, 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 one 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.

Materials 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 one week and one, three, six and twelve 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 one 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 pre-fracture information (T0) was gathered one week or one month after hip fracture by self- or proxy-reported questionnaires. The following data were collected at baseline within one 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 one week (T1), one month (T2), three months (T3), six months (T4) and one 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 (supplementary 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 one 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 (pre-fracture 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 pre-fracture 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.

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)
Pre-fracture living in institution (N,%)	151 (21.7)	140 (37.7)	11 (3.4)
Pre-fracture 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 pre-fracture 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). Pre-fracture frailty was associated with pre-fracture HS, adjusted for residential status as a confounder (β-0.29; SE 0.02; $p<0.001$; 95% CI -0.33, -0.26). 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 pre-fracture, 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, 1.734) experienced by frail patients over one year, compared with the problems in the non-frail group.

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

	Crude			Adjusted[a]		
EQ-5 Domain	**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 pre-fracture status of the EQ-5D domain, age, pre-fracture 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, -0.299) and self-rated health (β -21.9; 95% CI -24.2, -19.6) in elderly patients one 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, -0.069) for the association between frailty and health status, adjusted for deceased drop-outs and for confounders, including pre-fracture EQ-5D score, age, pre-fracture residential status, pre-fracture 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 pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia

[b] Adjusted for death

[c] Adjusted for death, and pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia

Abbreviations: EQ-5D: Euroqol 5 dimensions; EQ-VAS Euroqol Visual Analogue Scale; ICECAP-O: ICEpop CAPability measure for Older People; **β**: 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, -0.106; Table 3).

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 one 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 pre-fracture status of the EQ-5D domain, the major differences between frail and non-frail patients disappeared. Confounders, such as pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia, weakened also the association between frailty and QoL, but the association remained significant and clinically relevant. Our findings demonstrate that pre-fracture 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 pre-fracture 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 pre-fracture 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 pre-fracture frailty status and HS data were only collected in patients who flowed into the study until one 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 pre-fracture capability wellbeing. Second, frail patients showed a higher capability wellbeing score at one-week follow-up than at one-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 one 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 pre-fracture 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 one year after hip fracture, even after adjusting for pre-fracture HS, age, pre-fracture residential status, pre-fracture 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 pre-fracture frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

Contribution of authors:

CR, NK, LM, TG and MJ contributed to conception and design of this study. CR, ML, NK and LM contributed to the data collection. CR, ML, NK, LM and MJ contributed to the analyses and interpretation. CR, ML, NK, LM, JS, TG and MJ contributed to preparation of the manuscript. The final version of the article was approved by all the authors.

Competing interests: CR declares that he has no competing interest. ML declares that she has no competing interest. NK declares that she has no competing interest. LM declares that she has no competing interest. JS declares that she has no competing interest. TG declares that he has no competing interest. MJ declares that she has no competing interest.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has been approved by the Medical Ethics Committee Brabant, the Netherlands (project number NL50258.028.14).

Data sharing statement: Data could be shared after consultation with BIOS study group

Acknowledgements: Not applicable.

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Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

Figure 2. Patterns of health status according to frailty status over time.

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

Figure 4. Patterns of capability wellbeing according to frailty status over time.

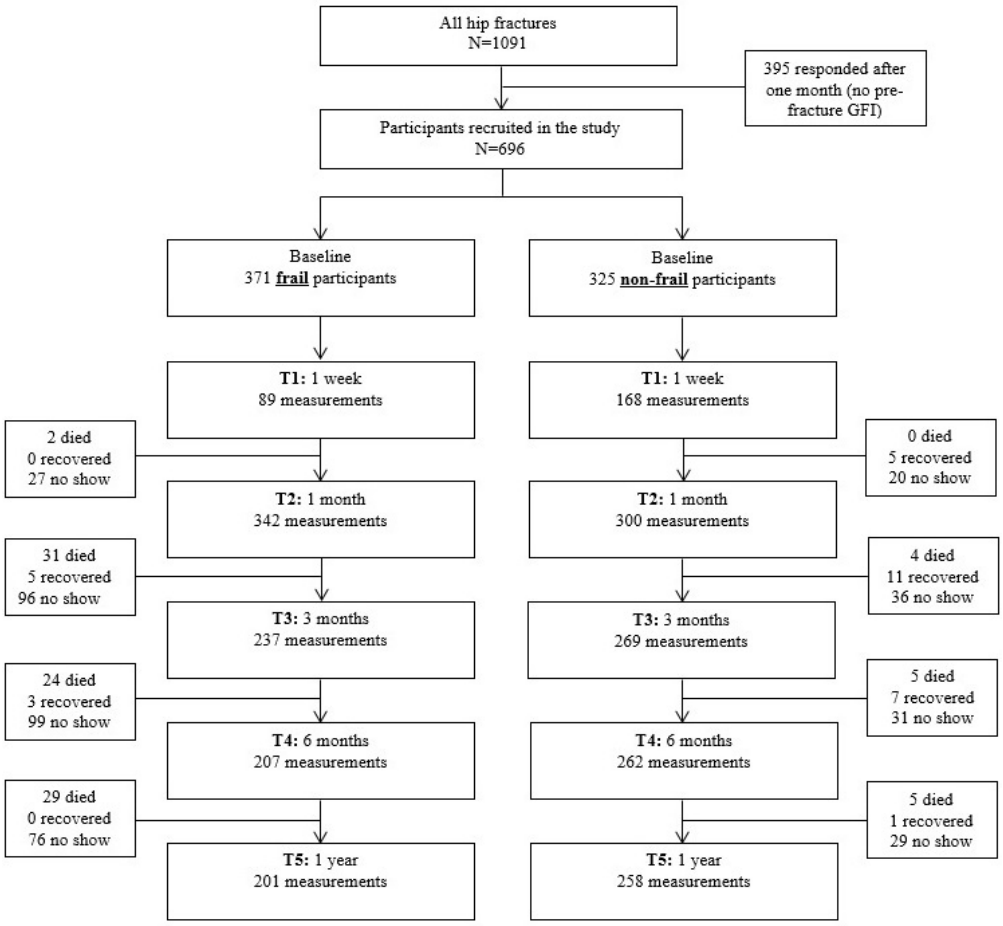

Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

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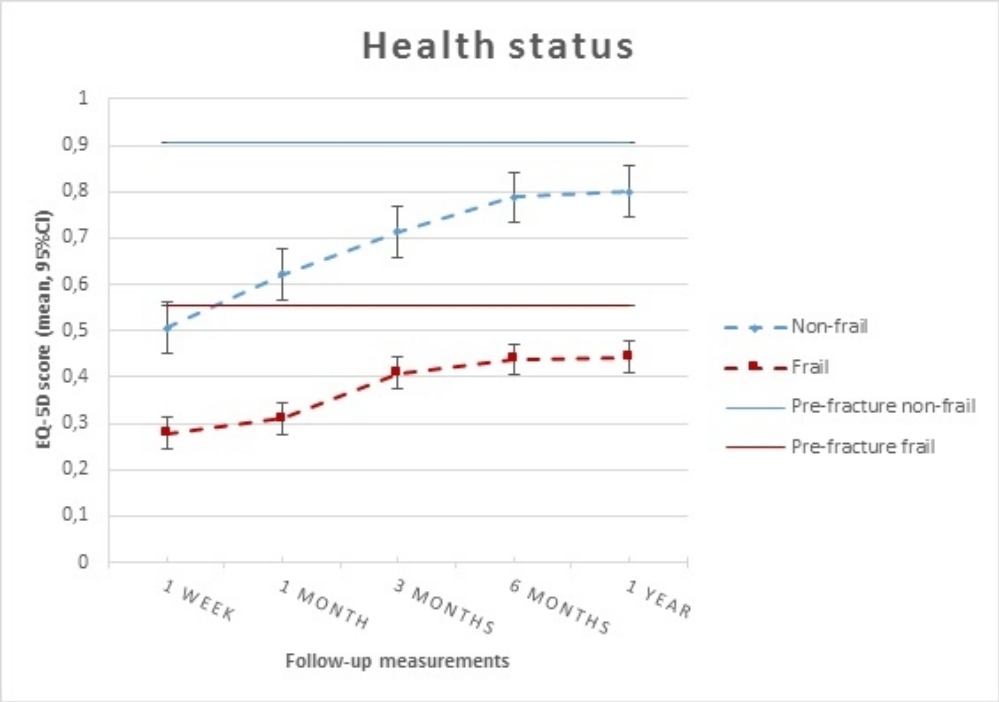

Figure 2. Patterns of health status according to frailty status over time

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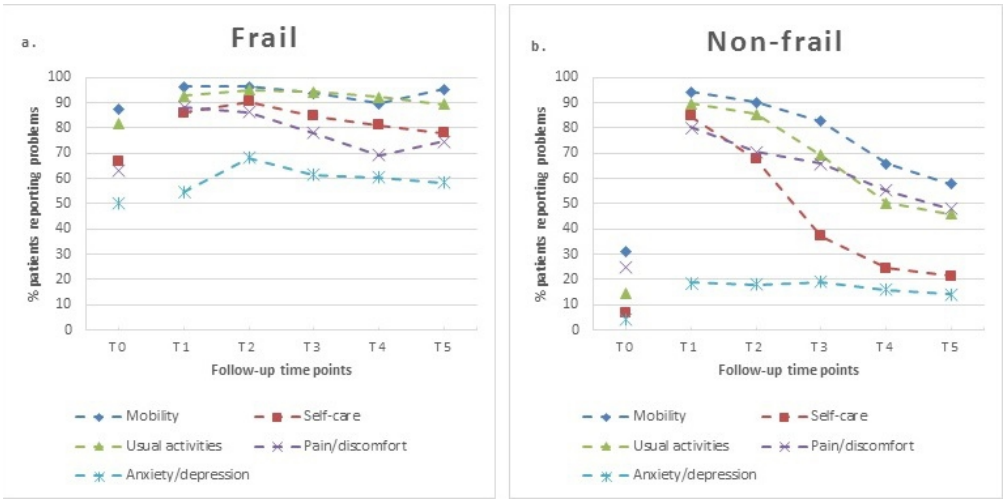

Figure 3. Percentage of frail (a) and non-frail (b) patients reporting problems on each EQ-5D-3L. questionnaire item at each follow-up time point.

64x32mm (300 x 300 DPI)

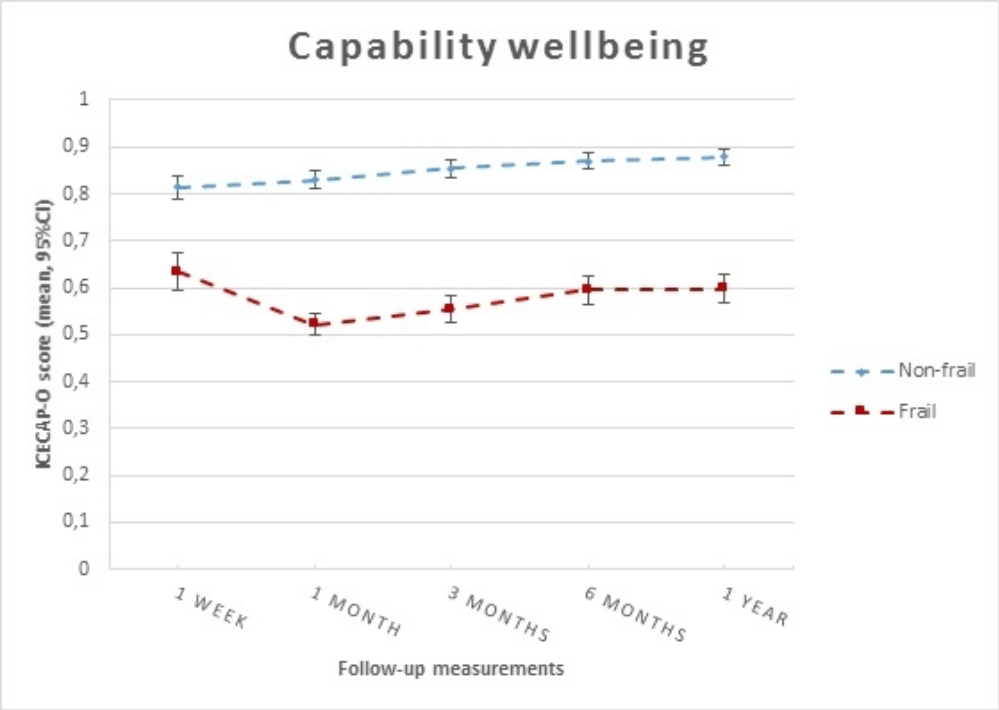

Figure 4. Patterns of capability wellbeing according to frailty status over time

47x33mm (300 x 300 DPI)

Supplementary 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

Reference: 16. Steverink N, Slaets J, Schuurmans H, Van Lis M. Measuring frailty: Development and testing of the groningen frailty indicator (GFI). Gerontologist. 2001;41(1):236.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.