Long-term mortality of patients with osteoarthritis after joint replacement: Prognostic value of pre- and postoperative pain and function

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ABSTRACT

Objectives

To investigate whether osteoarthritis (OA)–specific assessment values (i.e. Western Ontario and McMaster University Osteoarthritis Index [WOMAC]) and generic pain and function (visual analog scale [VAS], Hanover Functionality Status Questionnaire [FFbH]) measured before and 12 months after arthroplasty are associated with the risk of long-term mortality in a cohort of patients with advanced OA of the hip or knee.

Methods

The Ulm Osteoarthritis Study was a prospective cohort study of OA patients with unilateral total hip or knee replacement between January 1995 and December 1996. Correlation coefficients were calculated to describe the agreement between the different assessments. Mortality was assessed during the follow-up period (last update: July 2019). Cox proportional regression models were used to estimate hazard ratios (HRs) for mortality after adjusting for covariates.

Results

Arthroplasty was accompanied by a clear reduction in pain and improved function throughout all assessments in the 706 included patients. The results of the adjusted Cox models showed no relationship between baseline and follow-up joint-specific WOMAC assessments and long-term mortality. However, an independent increased risk of mortality was found with generic function assessments. In the final adjusted model, the HR for the 12-month follow-up value was 1.79 (95% confidence interval, 1.24–2.60) in the group with clinically relevant impairment versus the reference group.

Conclusions

Poor function based on the generic assessment was associated with increased long-term mortality, suggesting that functional impairments in daily life activities may be more important for long-term survival than OA-specific impairments in this patient group.

SIGNIFICANCE AND INNOVATIONS

- In our study population of patients with osteoarthritis (OA) of the hip or knee, we found a robust association of the generic assessment of functional impairment (that is, Hanover Functionality Status Questionnaire) with long-term mortality even after the adjustment for covariates in contrast to the OA-specific Western Ontario and McMaster University Osteoarthritis Index function assessment. An independently increased risk for subsequent mortality was found with preoperative and 12-month postoperative measurements.
- This results suggest that functional impairment in daily living may be more important for long-term survival than OA-specific impairments in patients with OA undergoing arthroplasty.

INTRODUCTION

Joint replacement is a common surgical procedure. In Germany, more than 400,000 primary hip and knee joint prostheses are implanted annually, making it among the most common operations.[1] The most common indication for joint replacement is osteoarthritis (OA), a disease of the musculoskeletal system characterized by degenerative destruction of the articular cartilage. In 2014, the lifetime prevalence of diagnosed OA in adults aged 18–79 years was 17.9%.[2] The prevalence of OA increases with age, and OA is more common in women than in men.[3]

OA is associated with functional impairments and joint pain, with the hip and knee joints being the most commonly affected.[4] Pain relief and functional improvement are the main reasons why patients undergo arthroplasty.[5] A 2017 study of more than 600 patients reported systematic improvement in all parameters for up to 12 months but especially at the 3-month follow-up after arthroplasty, with more than 70% of patients achieving good outcomes including improvement in pain, stiffness, and function.[6] In a study of 560 OA patients, the authors reported that changes in pain and function within the first 3 months after arthroplasty were particularly predictive of pain and functional status 2 years later.[7] Pain and functional improvements tend to peak within the first 12 months.[8,9]

Mortality associated with OA has been investigated, but the results are heterogeneous. A meta-analysis of nine studies worldwide found no reliable evidence between OA and all-cause mortality.[10] Another meta-analysis from Italy with data from seven studies and a mean follow-up of 12 years concluded that OA significantly increased the risk of death from cardiovascular diseases.[11] A meta-analysis of two cohort studies of patients with knee OA

from Sweden reported an inverse association with mortality only in the naive association without the correction for potential confounders.[12] An analysis published in 2018 by Büchele et al. reported no statistically significant increase in age-specific all-cause mortality in patients undergoing hip or knee arthroplasty compared to the general population during 20 years of follow-up.[13]

The influence of pain and function on mortality has rarely been studied. Insufficient research has compared OA-specific and generic assessments measuring pain and function and whether there are differences in their prognostic value for long-term mortality.

This study aims to investigate whether there is an association between pain and function using the OA-specific Western Ontario and McMaster Universities Arthritis Index (WOMAC), the generic Hanover Functionality Status Questionnaire (FFbH), and the generic visual analog scale (VAS) assessments preoperatively and 12 months postoperatively with long-term mortality. We also calculated the correlation between the different assessments to describe the agreement and better understand the possible differences in the results.

METHODS

Study design and study population

For the prospective cohort Ulm Osteoarthritis Study, patients who underwent unilateral total hip or knee arthroplasty due to advanced OA were recruited consecutively between January 1995 and December 1996 in four hospitals in Southwest Germany. The primary goals of the project were to improve the documentation and classification of degenerative joint diseases, further develop our knowledge of prognostic factors, and identify determinants of the course of the disease. The inclusion criteria (Caucasian race; age ≥75 years; absence of malignancy, inflammatory diseases, or corticosteroid medication; no previous joint replacement) were fulfilled by 809 patients who also provided written informed consent. The initial study[14,15], as well as the current follow-up, was approved by the Ethics Committee of Ulm University (no. 164/14). The study was conducted in accordance with the relevant guidelines and regulations and the Declaration of Helsinki.

Assessment of functionality and pain

Two different tools were used to assess function and pain. To measure function, the FFbH and the function subscale of the WOMAC were applied. The basic version of the FFbH (including 18 single questions regarding the last 7 days), a combined version of the FFbH-P (polyarthritis) and the FFbH-R (back pain) assessments, was used to assess general function. WOMAC (including 17 single questions) was used to specifically describe the function in the operated joint at the time of the assessment.

VAS and the pain subscale of the WOMAC were applied to measure pain in the affected knee or hip joint. Both measures describe pain in the operated joint at the moment of the

assessment; however, the WOMAC pain subscale concentrates on typical OA-associated circumstances. For comparability, each score was transformed to a scale from 0 (unimpaired function, no pain) to its maximum value (impaired function, extreme pain). The measurements were taken at baseline, immediately before joint replacement surgery, and 12 months after joint replacement.

To reduce the complexity of the data, we categorized all of the assessment variables. For the FFbH, the categorization followed the recommendations of the developers of each.[16] Accordingly, scores (after inversion) from 0% to 20% correspond to normal function. Scores from 21% to 30% correspond to moderate function, while scores from 31 to 40% indicate an abnormal finding, and scores above 40% indicate clinically relevant functional impairment. We modelled the classifications for the VAS and WOMAC pain assessments in points as performed in an earlier work with the same data by Stürmer et al (VAS groups: 0–58, 59–69, 70–78, 79–87, and 88–100; WOMAC pain groups: 0–8, 9–11, 12–14, and 15–20).[17] Quartiles were used for the WOMAC function assessment as described by Hawker et al.[18]

Assessments of morbidity and mortality

Morbidity at baseline was self-reported. We collected information about the history of physician-diagnosed comorbidities and symptoms (e.g., history of overweight, obesity, diabetes mellitus type 2, and gout). Mortality was determined during the follow-up period of up to 25 years via the residents' registration office. The last update was performed in July 2019. Further details can be found elsewhere.[13]

Handling of missing values

For each assessment, only patients with baseline values were included. Of them, WOMAC function values were missing for 250 patients (missing rate [MR]: 40%), WOMAC pain values were missing for 197 (MR: 30%), FFbH values were missing for 225 (MR: 33%), and VAS scores were missing for 400 (MR: 50%) at the 12-month follow-up.

We used multiple imputations for missing follow-up values using the full conditional specification, which uses chained equations. To provide imputations, the assumption of missingness at random was checked. For our data, we chose m=25 imputed datasets and T=30 iteration steps per dataset. The averaged values from the imputation led to an evaluable imputed study population (ISP).

Statistical analysis

We used two different approaches to analyze the correlation between functional impairment and pain intensity. Approach one combined the two WOMAC subscales for function and pain, while approach two combined the FFbH function score with the VAS pain score. To assess the trajectory of function and pain, the mean values of all assessments were calculated with the corresponding standard errors for baseline and follow-up.

We used Cox proportional hazards models to estimate the time to death as a function of categorized pain intensity and functional impairment at three different time points. The first time point considered the baseline values, the second considered the 12-month follow-up values, and the third considered the follow-up values with additional adjustment for baseline values.

Pain and function were included as separate exposure variables exposed in one Cox model in a simultaneous manner for each of the three time points. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by pooling according to Rubin‘s rule across the m=25 imputed datasets after multiple adjustments for sex (pre-defined covariate), age, body mass index (BMI), and localization of OA (knee or hip, also a pre-defined covariate). We considered an adjustment for the localization of OA necessary because of age and mortality differences between hip and knee patients (see supplemental **Table A.2.**). The selection of characteristics included in these analyses was based on a previous investigation of the same dataset.[13] The assumption of proportional hazards was confirmed for each model using Schoenfeld residuals.

The pooled correlations between the measured pain and function values were evaluated by Fisher Z-transformation using Spearman‘s rank correlation coefficients as a measure of agreement.

To verify sensitivity, all results based on the imputed data were compared with the original data to determine if the imputed results were plausible. All analyses were performed using R Studio version 4.0.2.

RESULTS

Overall, 706 patients were included in the ISP; of them, 179 (25.4%) men had hip OA and 95 (13.5%) had knee OA (total men, n=274 [38.8%]). Of the 432 women (61.2%), 189 (26.7%) had hip OA and 243 (34.4%) had knee OA. As displayed in **Table 1**, the median patient age in the ISP at baseline was 65 (quartile 1 [Q1] to quartile 3 [Q3]: 58–70) years. All study patients underwent at least unilateral total joint replacement for hip or knee OA when considered for this study (but no history of previous joint replacement); of them, most (n = 546 [77.3%]) had bilateral OA. After 25 years of follow-up, 458 (64.9%) patients died in the ISP group. The median observation period was 19 (Q1–Q3: 12–23) years, and the mortality rate was 38 (95% CI: 35–42) per 1,000 person-years.

The mean preoperative values indicated relevant pain (WOMAC pain: 11.8 [standard deviation (SD): 3.4], range: 0–20 points, and VAS: 72.0 [17.0], range: 0–100 points) and functional impairment (WOMAC function: 38.6 [11.4], range: 0–68 points, and FFbH: 32.7% [15.7%], range: 0%–100%). The values were more favorable at the 12-month follow-up. The measured mean values at 12 months after surgery were significantly decreased compared to the preoperative values, showing very low pain levels (WOMAC pain: 4.6 points [4.1; 61% decrease] and VAS: 15.0 points [20.9; 79% decrease]) or normal functionality (WOMAC function: 19.0 points [14.9; 51% decrease] and FFbH: 20.2% [16.2%; 38% decrease]). This change was also reflected in the distribution of the patients among the categories, in which the number of patients in the category with the lowest functional impairment and pain after surgery increased significantly across all assessments, whereas the patients were almost equally distributed among the categories preoperatively. Looking at the subpopulations stratified by sex and OA localization, the median age of patients with knee OA was 5 years

older than that of patients with hip OA, and more patients of both sexes who underwent arthroplasty of the knee joint died (**Supplement Table A.2**).

As depicted in **Table 2**, the correlation of the WOMAC assessments for pain with function was rho=0.68 for baseline and follow-up, indicating a medium to strong linear correlation between pain and function values. In contrast, the correlations between the generic assessments of pain and function were rho=0.21 for baseline and rho=0.23 for follow-up, indicating a weak linear correlation.

The results of the adjusted Cox models showed no significant relationship between baseline and follow-up between joint-specific WOMAC measurements and long-term mortality (**Table 3**) since all 95% CIs included the null effect value of one and the p-value of the trend test was relatively large. However, follow-up WOMAC function measurements showed increased HRs with increasing categories, but the 95% CI also included the zero-effect value, and the test for trend in the simultaneous model was p=0.11.

The results of the VAS and FFbH as generic assessments (**Table 4**) showed a different pattern. Higher FFbH measurements were associated with higher mortality, and the higher the FFbH measurements (i.e., the higher the functional impairment), the higher the associated HR. At baseline, the results of the simultaneously adjusted model were statistically significant only for the FFbH categories. In the group of patients with values of 31% to 40%, the risk of mortality was increased by 38% (HR 1.38, 95%CI 1.03-1.84), whereas patients in the top category had a 51% higher risk of mortality than patients with normal function (HR 1.51, 95% CI 1.15–1.98, p for trend <0.01) compared to the reference category.

Considering only the measurements at 12 months post-arthroplasty, patients with moderate FFbH functional impairments had a 52% higher mortality risk (HR 1.52, 95% CI 1.10–2.08), while patients with abnormal findings had a 55% higher mortality risk (HR 1.55, 95% CI 1.06–2.26), and patients with clinically relevant functional impairments had a 2.03 times higher mortality risk than patients with normal function (HR 2.03, 95% CI 1.45–2.84, all $p<0.05$ for all).

Consideration of the 12-month values after the adjustment for baseline values revealed that the mortality risk was 43% higher in patients with moderate functional impairments (category 21% to ≤30%) and 79% higher in patients with clinically relevant functional impairment (category ≥41%) (HR 1.43, 95% CI 1.02–2.00 and HR 1.79, 95% CI 1.24–2.60).

In addition to the simultaneous models, the supplement (**Tables A.4** and **A.5**) contains single models in which pain and function were calculated separately in one Cox model. The results are generally very similar to those of the simultaneous models. The only notable difference was observed at baseline. In this study, there was an association between severe pain and mortality. Patients with the most severe pain (i.e., ≥ 88 points) had an HR of 1.43 (95% CI 1.04–1.98) compared with patients in the reference group with low pain after the adjustment for covariates ($p=0.01$ for trend).

Notably, the adjusted covariates of the simultaneous model of the generic assessments showed that the mortality risk for a 1-year increase in age was 12%, and women had a 40–46% lower mortality risk than men (data not shown).

Examination of the prognostic value showed that the HRs of the WOMAC baseline values in the simultaneously adjusted model were close to those in the baseline model. The same was evident for the HRs of the VAS values. In contrast, the HRs of the FFbH baseline values differed strongly between baseline and the simultaneously adjusted model and showed no statistically significant increase in HRs.

The results of the sensitivity analysis of only complete cases showed quite similar results (**Supplemental Tables A.1** and **A.3**), although point estimates of the imputed dataset showed a slightly stronger association with long-term mortality (**Supplemental Tables A.4** and **A.5**). Also when we when included diabetes mellitus as well as cardiovascular diseases (i.e. hypertension, myocardial infarction, congestive heart failure) into the models only minor changes in the point estimates associated with pain and function occurred.

DISCUSSION

In this prospective cohort study of 706 evaluable patients undergoing knee or hip arthroplasty, we found that, at 1 year after surgery, all pain and functional impairments decreased considerably compared to the preoperative values. We found no statistically significant association between the WOMAC arthritis-specific assessments and long-term survival, either when preoperative values or 12-month values were considered. Notably, the WOMAC was not intended to predict mortality. However, we found a strong dose-response relationship with the more generic FFbH function score values at both time points, suggesting that functional impairment in daily living may be more important for long-term survival than OA-specific impairment in this group of patients.

In line with our observations, surgical intervention on the knee and hip joints of OA patients resulted in considerable pain relief and functional improvement even 12 months after arthroplasty, which Scott and colleagues cited as the main reasons for joint replacement.[5] Similarly, our investigations underline the results of the meta-analyses by Shan et al. of significant benefits in daily functional activities after hip and knee joint replacement.[19,20] Similar postoperative improvements in pain and functional results were also observed by Ethgen et al.[21] Earlier studies also showed that function increased and pain subsided after arthroplasty, in which improvement was more pronounced after hip operations.[22–24]

The prognostic value of assessments with long-term survival is strongly dependent on measurement method. For example, no increased association with mortality was found in the WOMAC assessments, whereas the generic FFbH assessment demonstrated an increased association almost throughout. This suggests that general functional impairments in daily

life, which include difficulties with physical care or simple movements (e.g., picking up objects or dressing), play a more important role in long-term survival than disease-specific consequences and may, therefore, be a beneficial intervention target. Nüesch et al. reported that a history of diabetes, cancer, or cardiovascular disease increased functional impairment such as severe walking disability (the latter in a dose-respone relationship) and led to an increased risk of death among OA patients.[25] The authors concluded that the management of patients with OA should focus on effectively treating CVD risk factors and comorbidities and increasing physical activity. Our data showed that, in the categories with deteriorating function values, mortality tended to increase linearly.

In contrast to our observations, Hawker et al. reported that patients with hip or knee OA over a follow-up of 13 years were associated with all-cause mortality based on the WOMAC functional instrument but not with WOMAC pain.[18] The differences with our results might be explained by the fact that all patients in our study underwent arthroplasty in contrast to Hawker et al. However, another study from Denmark reported that patients with chronic pain had a 39% higher mortality rate than the general population.[26] Recent studies on pain and mortality in adults over 50 years of age reported that pain that interferes with activities of daily living is particularly associated with an increased risk of mortality.[27]

Age and male sex were other main factors associated with an increased risk of mortality at all measurement points. However, we did not find a robust association between survival and localization of OA, although most knee prosthesis patients showed significantly worse values than hip prothesis patients. Presumably, the effect is reflected in the significant age differences since the group of knee patients was also a median 5 years older. In addition, we

did not find a relationship between BMI and mortality. Büchele et al. came to the same conclusion in an earlier analysis that considered only baseline values.[13]

Analyzing the WOMAC assessments specifically applied to OA patients, we found a strong correlation between pain and function (see **Table 2**). The values of the two assessments were comparable, and the function score increased proportionally to the pain score at both measurement points. However, no association with survival was observed (see **Table 3**).

In comparison, the generic assessments showed only a very weak correlation and might measure very different aspects. Thus, the function score increased only slightly with the pain score, which was underlined by low agreement values at both time points. The differences in mortality between scores may have instrument-related reasons. A meta-epidemiological study of 44 randomized comparative trials with 15,556 patients underlined our assumption and showed in the direct instrument comparison that the VAS had higher test sensitivity than the WOMAC pain scale at detecting treatment effects at the individual trial level, although the differences were relatively small.[28]

One of the strengths of this study is that we included a study population of more than 800 patients, 706 of whom were evaluated. We achieved this high number of evaluable patients by using multiple imputations to add each missing follow-up value to the corresponding baseline value. The results of the complete case analysis support our conclusions of the imputed study.

Another strength of this study was that many different assessments were collected that were specifically designed for OA and included general pain and function assessments that enabled direct comparisons. It should also be emphasized that this study had a long follow-up period of 25 years, which provides almost complete coverage in terms of the assessment of vital status. In the next study, it might be important to identify the associated factors, which might offer a target for early intervention and preventive actions. However, it is also possible that many of these impairments may not be causal and may be the only markers of underlying comorbidities.

As limitations, the data did not reveal the exact cause of death. In addition, values were missing for the follow-up measurements and not imputed. However, our sensitivity analysis did not indicate the introduction of specific bias. Furthermore, the comorbidity data were also rather crude (e.g., diabetes yes/no). We did not adjust for severe disease because OA patients with cancer or other malignancies were excluded from the study.

In conclusion, our results suggest that poor function based on the generic FFbH assessment is generally associated with an increased risk of long-term mortality, while generically assessed pain and OA-specific WOMAC measurements were not associated with long-term mortality, suggesting that general health issues may be more important for long-term survival in this group of patients than OA-specific impairments. Therefore, activities targeting functional capacity and improvements in daily activities may be beneficial for improving overall survival. [3,733 words]

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Table 1: Patient characteristics at baseline. n number of patients; Q1 first quartile; Q3 third quartile.

Characteristics	**Imputed study population (ISP) N=706**	
Women, *n* (%)	432	(61.2%)
Localization of OA		
- Female hip, *n* (%)	189	(26.7%)
- Male hip, *n* (%)	179	(25.4%)
- Female knee, *n* (%)	243	(34.4%)
- Male knee, *n* (%)	95	(13.5%)
Age (years; Median, Q1-Q3)	65	(58-70)
BMI (kg/m²; Median, Q1-Q3)	28.0	(25.6-30.9)
Smoking: Former Smoker, *n* (%)	215	(30.5%)
Current smoker, *n* (%)	90	(12.7%)
History of overweight/obesity, *n* (%)	404	(57.2%)
Diabetes mellitus type 2, *n* (%)	64	(9.1%)
Gout, *n* (%)	83	(11.8%)
Hypertension, *n* (%)	363	(51.4%)
Myocardial infarction, *n* (%)	30	(4.2%)
Congestive heart failure, *n* (%)	133	(18.8%)
Cholesterol (mmol/l; Median, Q1-Q3)	5.7	(5.1-6.3)
Uric acid (mmol/l; Median, Q1-Q3)	315	(266.2-375.0)
hs-CRP (mg/l; Median, Q1-Q3)	2.5	(1.2-5.0)
Bilateral OA, *n* (%)	546	(77.3%)
Unilateral OA, *n* (%)	103	(14.6%)

Unknown, *n* (%)	57	(8.1%)
Generalized OA, *n* (%)	148	(21.0%)
Not-generalized OA, *n* (%)	427	(60.5%)
Unknown, *n* (%)	131	(18.6%)
Secondary OA, *n* (%)	255	(36.1%)
Primary OA, *n* (%)	432	(61.2%)
Unknown, *n* (%)	19	(2.7%)
25 years of follow-up		
Deceased, *n* (%)	458	(64.9%)
Observation time (years; Median, Q1-Q3)	19.0	(12.2-23.0)
Mortality rate per 1,000 person years (95%-CI)	38	(35-42)

Table 2: Measurement of agreement between pain and function: Pooled Spearman's rank correlation of arthrosis-specific WOMAC, and generic VAS/FFbH.

Legend: FU – follow-up, WOMAC: Western Ontario and McMaster University Osteoarthritis Index, VAS: Visual Analogue Scale, FFbH: Hanover Functionality Status Questionnaire.

Correlations (rho pooled)	WOMAC function		FFbH (function)	
	Baseline	12 month FU		
WOMAC pain	**0.68,** p<.001 N=625	**0.68,** p<.001 N=625		
			Baseline	12 month FU
VAS (pain)			**0.21,** p<.001 N=677	**0.23,** p<.001 N=677

Table 3: Hazard Ratios (HR) of WOMAC assessments with long-term mortality (95%-confidence intervals (CI) and p-values): Simultaneous models with pain and function at the three various time points (baseline, 12-month follow-up and 12-month follow-up with baseline adjustment).

Description: All models adjusted for age, sex, localisation of OA and BMI; WOMAC- Western Ontario and McMaster University Osteoarthritis Index; ref-reference.

	Baseline	
		(p-value for trend)
	HR	**95%-CI**
WOMAC pain & WOMAC function		
WOMAC pain (points)		*(p=.80)*
≤ 9 (ref.)	1.00	-
>9-≤11	1.08	0.80-1.46
>11-≤14	0.96	0.69-1.34
>14	1.12	0.76-1.63
WOMAC function		*(p=.32)*
1st quartile (ref.)	1.00	-
2nd quartile	0.79	0.59-1.04
3rd quartile	0.92	0.66-1.30
4th quartile	1.17	0.81-1.69

	12-month follow-up (without adjustment for baseline)	
		(p-value for trend)
	HR	**95%-CI**
WOMAC pain & WOMAC function		
WOMAC pain (points)		*(p=.55)*
≤ 9 (ref.)	1.00	-
>9-≤11	0.90	0.55-1.47
>11-≤14	0.99	0.51-1.93
>14	0.74	0.32-1.69
WOMAC function		*(p=.11)*
1st quartile (ref.)	1.00	-
2nd quartile	1.23	0.78-1.94
3rd quartile	1.34	0.64-2.78
4th quartile	1.67	0.87-3.21

	12-month follow-up (adjusted for baseline)	
		(p-value for trend)
	HR	**95%-CI**

WOMAC pain & WOMAC function		
WOMAC pain (points)		*(p=.51)*
≤ 9 (ref.)	1.00	-
>9-≤11	0.87	0.53-1.44
>11-≤14	0.97	0.49-1.94
>14	0.71	0.30-1.66
WOMAC function		*(p=.16)*
1st quartile (ref.)	1.00	-
2nd quartile	1.25	0.77-2.02
3rd quartile	1.36	0.63-2.94
4th quartile	1.53	0.77-3.05

Table 4: Hazard Ratios (HR) of the generic assessments (VAS/FFbH) for long-term mortality (95%-confidence intervals (CI) and p-values): Simultaneous models with pain and function at the three various time points (baseline, 12-month follow-up and 12-month follow-up with baseline adjustment).

Description: All models adjusted for age, sex, localisation of OA and BMI; bold marked: significant mortality and p trend results (p<0.05); FFbH Hanover Functionality Status Questionnaire; VAS- Visual Analogue Scale; ref-reference.

	Baseline	
	HR	*(p-value for trend)* **95%-CI**
VAS & FFbH		
VAS (points)		*(p=.07)*
≤58 (ref.)	1.00	-
59-≤69	1.06	0.78-1.44
70-≤78	1.03	0.75-1.41
79-≤87	1.19	0.87-1.64
≥88	1.32	0.96-1.83
FFbH (%)		***(p<.01)***
≤20 (ref.)	1.00	-
21-≤30	1.30	0.97-1.74
31-≤40	**1.38**	**1.03-1.84**
≥41	**1.51**	**1.15-1.98**
	12-month follow-up (without adjustment for baseline)	
	HR	*(p-value for trend)* **95%-CI**
VAS & FFbH		
VAS (points)		*(p=.21)*
≤58 (ref.)	1.00	-
59-≤69	0.92	0.40-2.14
70-≤78	0.84	0.33-2.11
79-≤87	0.51	0.08-3.03
≥88	0.46	0.10-2.22
FFbH (%)		***(p<.01)***
≤20 (ref.)	1.00	-
21-≤30	**1.52**	**1.10-2.08**
31-≤40	**1.55**	**1.06-2.26**
≥41	**2.03**	**1.45-2.84**
	12-month follow-up (adjusted for baseline)	

	HR	*(p-value for trend)* 95%-CI
VAS & FFbH		
VAS (points)		*(p=.20)*
≤58 (ref.)	1.00	-
59-≤69	0.91	0.38-2.17
70-≤78	0.87	0.34-2.22
79-≤87	0.48	0.08-2.90
≥88	0.44	0.09-2.11
FFbH (%)		***(p<.01)***
≤20 (ref.)	1.00	-
21-≤30	**1.43**	**1.02-2.00**
31-≤40	1.41	0.94-2.13
≥41	**1.79**	**1.24-2.60**