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Dementia and CSF-Biomarkers for Alzheimer's Disease Predict Mortality after Acute Hip Fracture

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ABSTRACT

Background: Mortality is high after an acute hip fracture (AHF) surgery. Are cognitive impairment and/or altered levels of Alzheimer's Disease (AD)-biomarkers in cerebrospinal fluid (CSF) predictors of mortality in AHF-patients, as retrospective studies indicate?

Methods: Prospective single-center study including 373 AHF-patients, operated in spinal anesthesia. Cognitive status was evaluated by Clinical Dementia Rating (CDR); CSF was analyzed for AD-biomarker concentrations (total tau (T-tau), phosphorylated tau (P-tau), amyloid beta ratio (Aβ42/Aβ40). CDR and biomarker levels were related to mortality up to one-year post-surgery, using univariate logistic regression analysis.

Results: Survival analyses showed that mortality was associated to the degree of dementia. In the entire patient cohort 30-, 90-, and 365-day mortality rates were 7.2%, 15.5%, and 25.5%, respectively, but only 2.7%, 5.5%, and 12.6%, for cognitively intact *vs.* 16.3%, 31.7%, and 42.3% for demented patients (OR=2.2–2.8 [CI=1.6–4.9]; *p*=0.0001). High CSF T-tau (OR=1.19 [CI=1.05–1.33]; *p*=0.004) and low Aβ42/Aβ40-ratio (OR=0.85 [CI=0.74–0.97]; *p*=0.017) were associated with increased 90-day mortality. Analysis of 4 subgroups (Cognitive impairment +/- and Biomarkers +/-) showed significant associations of dementia and CSF biomarker concentrations to mortality after an AHF. Even cognitively intact patients presenting with abnormal AD-biomarkers showed an increased 90-day mortality which, however, was statistically insignificant.

Conclusions: Cognitive impairment and altered CSF biomarker concentrations indicative of AD pathology can predict increased mortality in patients with an AHF, and so probably even before clinical dementia diagnosis by early biomarker analysis; a notion that may have substantial clinical implications by improving perioperative treatment and postoperative rehabilitation.

EDITORIAL COMMENT

This observational study assessed biomarkers for pre-senile dementia in cerebrospinal fluid sampled at spinal anesthesia for acute hip fracture surgery and pre-injury cognitive status, along with relations to follow-up for mortality up to 1 year after operation. Both degree of dementia and biomarker levels were associated with higher post-operative mortality after acute hip fracture and repair.

INTRODUCTION

An acute hip fracture (AHF), the second most common orthopedic fracture type in Scandinavia (and other regions), represents a major trauma, affecting elderly, often frail, patients,[1-4] with considerable risk for poor outcome. Mortality is high, 7–11% at 30 days, 10–20% at 90 days, 25–40% at one year, and about 50% three years after surgery.[5-9] The patient's autonomy and quality-of-life is often restricted after AHF.

The majority of these patients have an American Society of Anesthesiologists Physical Status (ASA-SP)[10]-class of III-IV with high impact on mortality. There is a considerable prevalence of cognitive impairment, dementia or acute delirium, often enhanced by the fracture pain.[11] Cognitive impairment increases *per se* the risk of falling,[12] and thus fracturing the hip.[1,13] Dementia seems to be associated with increased mortality after AHF-repair,[7,14] and qualifies as risk factor in the Nottingham Hip Fracture Score (NHFS).[15,16]

Presently, we have well established cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease (AD), the most common form of dementia. Reflecting the core pathology of the disease, they include total tau (T-tau), a marker of neuronal and axonal degeneration, phosphorylated tau (P-tau), a marker of neurofibrillary tangle pathology,[17] and the 42-amino acid form of amyloid beta (Aβ42), a marker of plaque pathology (with lower concentrations in lumbar CSF due to retention of the protein in plaques in the brain).[18,19] CSF T-tau and P-tau, as well as the Aβ42/Aβ40 ratio, are used to verify underlying AD pathology in patients with cognitive symptoms.[20-22] Their combined use is more accurate and allows a differentiation of AD from other diseases, with sensitivity and specificity of 80–90%.[18] We know that abnormal reduction of CSF Aβ42-concentration can be seen decades before clinical AD-onset,[23,24] whilst CSF T-tau and P-tau pinpoint downstream onset of neurodegeneration and tangle formation closer (but still prior) to clinical presentation.[23-25]

In this prospective study, we wanted to investigate in a cohort of patients with AHF, 1) if those presenting with different degrees of cognitive impairment had higher mortality rates than those without this condition, and 2) if concentrations of CSF biomarkers for AD pathology were related to mortality.

MATERIALS AND METHODS

Ethical Considerations

This study, conducted in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice, was registered in Clinical Trials (NCT02409082) and approved by the Regional Ethical Committee of Gothenburg, Sweden (Dnr.350-13). Informed written consent was obtained from the participating patients, or their next-of-kin, if the patient was unable to give consent.

Patients

All patients admitted with an AHF to Sahlgrenska University Hospital, Mölndal, Sweden, from October 2013 to June 2015, were eligible for this study, if receiving spinal anesthesia and being operated - for laboratory accessibility - on weekdays (7 am to 6 pm) outside vacation periods. Patients with peri-prothetic, pathological, or conservatively treated fractures were excluded. Data on mortality were collected from the Swedish national patient registry. We had no control group in this study, but compared our results with an age- and gender-matched cohort, based on statistic data from the Swedish population registry.

Assessments of cognitive impairment and somatic status

Before premedication and surgery, the patient or - for cognitively impaired patients - their next-of-kin, were interviewed regarding the patient's pre-fracture cognitive status, using the Clinical Dementia Rating (CDR),[26] with focus on the period immediately prior to the trauma.
The CDR, originally developed for AD,[26] allows the assessment of six independent categories (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care), where memory is considered the primary category,[26] resulting in five possible scores: CDR:0 = normal; CDR:0.5 = mild cognitive impairment (MCI); CDR:1 = mild; CDR:2 = moderate; CDR:3 = severe dementia.
At admission to the hospital, patients were assessed by the Abbreviated Mental Test (AMTS).[27] AMTS, mainly validated in the elderly,[28] consists of ten short questions, where a score of less than 8 suggests a cognitive impairment at the time of testing. By omitting psychometric components, it is easier to conduct in these patients, than the Mini Mental Test.[29,30]

The somatic status at admittance was evaluated according to the ASA-PS-class[10] and the Nottingham Hip Fracture Score (NHFS).[16]

ASA-PS-class [10] is a five-category physical status classification system for assessing the fitness of patients before surgery, where ASA:1 indicates a completely healthy person and ASA:5 a moribund patient, not expected to survive 24 hours.

NHFS is a 10-points scale, scoring 0-4 points for "age" and 1 point each for: "male sex", "AMTS less than 7" (*i.e.* dementia), "admission hemoglobin less than 100 g/l", "living in institution", "at least two comorbidities", and "malignancy". Scores over 6 predict a significantly higher 30-day mortality.[16,31]

Cerebrospinal fluid (CSF) collection and analyses

CSF samples of 4–5 ml were obtained by lumbar puncture with a 24-G spinal needle in the L3–L4 or L4–L5 intervertebral space immediately before injection of the local anesthetic agent. CSF was collected in polypropylene tubes and transported directly to our biochemical laboratory, close to the operating center. After cell count, CSF was centrifuged at 1800 g. The supernatant was aliquoted in polypropylene vials, immediately frozen and stored at -80°C until analysis in the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden. CSF T-tau and P-tau concentrations were measured using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium). Aβ40 and Aβ42 concentrations were measured using the MSD Abeta Triplex assay (MSD, Rockville, Maryland) that specifically measures Aβ fragments ending at amino acid 38, 40, and 42. The results were used to calculate the Aβ42/Aβ40-ratio, which by normalizing each individual's Aβ production, performs better than Aβ42 alone to detect Aβ-pathology in the brain.[22] All CSF measurements were performed in one round of experiments using one batch of reagents, by board-certified laboratory technicians, who were blinded to clinical data. Intra-assay coefficients of variation were below 10%.

Statistical analyses

Data analysis with SAS for Windows (version 9.4) was performed by statistical consultants (Statistiska Konsultgruppen, Gothenburg).

Descriptive statistics are shown as number of cases and percentages for categorical variables, or mean (± standard deviation) and median (min–max) for continuous variables.

The Spearman Correlation Coefficient was used for correlation analysis between CDR and biomarkers. Biomarker cut-offs were based on an earlier study for CSF T-tau [24] and mixture modeling for the CSF Aβ42/Aβ40-ratio using the package mixtools [32] in R version 3.4.0 (R Core Team, 2013. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.). Values for the Aβ42/Aβ40-ratio > 0.064 were defined as normal, and

≤ 0.064 as abnormal. This unsupervised cut-off was established at the point that best separated the two groups defined in the bimodal histogram distribution.

The Kaplan–Meier curve was used to illustrate postoperative mortality in different patient groups. To determine the effect on overall survival, both demographic and clinical variables were evaluated with Univariate Cox Proportional Hazards Regression Analysis. The effect of survival at 30-, 90-, and 365-days was determined by logistic regression and presented as odds ratio (OR) and its 95% confidence interval (CI).

A two-tailed *p*-value of <0.05 was considered significant.

RESULTS

Patients

Totally 440 patients were eligible for this investigation. We excluded 67 patients, who were operated outside office hours (n=36), had missing CSF samples for technical (n=17) or medical (n=11) reasons, were re-operated on the other hip (n=2), or demanded a study withdrawal (n=1). Finally, 373 patients were enrolled into the study (Figure 1). There was no difference in demographic or clinical characteristics between enrolled (n=373) and excluded (n=67) patients. The average time between fracture diagnosis and surgery was 26 hours. Table 1 shows baseline characteristics of the studied patient cohort: 373 patients, mean age 83 years, 74% women. High predictable risk for surgery (ASA:3-4) was found in 47% (n=175). Further, 36% (n=135) had a NHFS score of at least 6, while 18% (n=68) scored 7 or more. Most patients (49%) were cognitively intact (CDR:0), while 23% presented a mild cognitive impairment (CDR:0.5), and 28% had a mild to severe dementia (CDR:1–3).

Mortality

The overall post-surgical mortality rate was 7% at 30 days, 16% at 90 days, and 25% at 365 days, respectively. We noticed a 2.6 times higher mortality in our patient cohort *vs.* an age- and gender-matched Swedish control group (Table 2).

Mortality and Clinical Dementia Rating

CDR-related mortality (Figure 2) was enhanced in patients with MCI (CDR:0.5), and even more in patients with manifest dementia (CDR:1–3). The 90-day mortality rate was 5.5% in the cognitively intact group (CDR:0) *vs.* 17% in patients with MCI (CDR:0.5), and finally 32% in patients with manifest dementia (CDR:1–3). Subgroup analysis (Table 3) shows 4 to 6 times higher 30-, 90- and 365-day mortality in demented (CDR:1–3) compared to cognitively intact (CDR:0) patients, with OR of 2.70 (CI=1.6–4.5), 2.75 (CI=1.9–3.9), and 2.33 (CI=1.7–3.0) (p=0.0001 for all 3 groups).

Mortality and *CSF biomarkers*

When comparing CSF biomarker concentrations, we found a difference of mean and median values in T-tau and the Aβ42/40 ratio, between patients alive and dead at 90- and 365-days post-surgery (Table 4). Univariate logistic regression analysis (Table 5), revealed a significant congruence of CSF biomarker concentrations to 90-day mortality, where increased T-tau and decreased Aβ42/Aβ40-ratio were associated with higher mortality risk (OR=1.19 [CI=1.05–1.33]; *p*=0.004, and OR=0.85

[CI=0.74–0.97]; *p*=0.017, respectively). Further, one year after surgery, this analysis showed a significant association between mortality rate and concentrations of T-tau (OR=1.14 [CI=1.03-1.27]; *p*=0.014). There was no correspondence found between the mortality rate and CSF-concentrations of p-tau. Finally, we could not show any significant association between CSF biomarker concentrations and 30-day mortality.

Mortality rate in subgroups

To exclude any impact of eventual head trauma on measured T-tau concentrations, we distributed patients into 4 subgroups (A–D), referring to the results in CDR and Aβ42/Aβ40-ratio:

Cognitively normal patients (CDR=0) (n=183) with

A) normal Aβ42/Aβ40-ratio (n=102)

B) abnormal Aβ42/Aβ40-ratio (n=81)

Cognitively impaired patients (CDR>0) (n=190) with

C) normal Aβ42/Aβ40-ratio (n=61)

D) abnormal Aβ42/Aβ40-ratio (n=129)

Mortality at 30- and 90-days post-surgery was low (2-3%) in group A, but twice respectively three times higher in group B (Table 6a). The 30- and 90-day mortality was 5 respectively 8 times higher in the groups showing various degrees of cognitive impairment (groups C, D), compared to those cognitively intact (group A). Furthermore, the 365-day mortality was 3 times higher in patients with dementia.

Univariate logistic regression showed statistically significant Odds Ratios of 6.5, 11, and 4.5 for 30-, 90-, and 365-day-mortality for demented patients (groups C, D) related to cognitively intact patients (group A). These differences were less prominent, but still statistically significant for 90- and 365-day-mortality, when adjusted for age (Table 6b and c).

DISCUSSION

Mortality is high after operation of acute hip fractures. Retrospective studies indicate that dementia increases the risk to die in patients with AHF. This prospective study investigated the relations between cognitive impairment, AD-biomarkers, and mortality in patients operated for AHF.

Specifically, we demonstrated significant associations between 1) cognitive impairment (*i.e.* MCI or dementia classified by CDR) and mortality, as well as 2) concentrations of AD biomarkers in CSF (*i.e.* Aβ42/Aβ40 and T-tau) and mortality, where decreased Aβ42/Aβ40-ratio and enhanced T-tau CSF concentrations – corresponding to changes found in AD – positively corresponded to increased mortality. Further, subgroup analysis revealed that patients with CDR>0 and positive AD-biomarkers had eight-fold higher mortality at 90 days, and three-fold higher mortality at one year, compared to cognitively intact patients.

All study patients received spinal anesthesia (with Bupivacaine and Fentanyl), as is routine for 85% of AHF-patients in our department. There are no large prospective studies demonstrating any advantage of neuro-axial or general anesthesia on mortality[9], and the effects of anesthesia *per se* were not further scrutinized in this investigation.

Overall mortality in our study corresponded to mortality rates observed by others after an AHF.[5-7,9] Several known factors contributing to mortality – as age, male gender, and ASA-PS-class – are part of risk evaluation systems, which have been validated on a great number of patients.[31,33] Dementia renders one out of ten points in the NHFS,[16] the only validated scoring system including cognitive function in AHF-patients.

However, clinical observations and previous retrospective studies[7,8,11,14,34] have suggested a higher impact of cognitive impairment on mortality in these patients.

One unique prospective study[35] presented their own predictive model, including age, gender, ASA-PS-class, and the Short Portable Mental Status Questionnaire (SPMSQ).[36] Thus, to combine ASA-PS-class – focusing on somatic status – with other screening models, could more accurately predict post-operative mortality risk for AHF.

In accordance with this, our prospective study demonstrated a strong congruence between degree of cognitive impairment and mortality after an AHF. We found that mortality in mentally intact patients was 2.7% at 30 days and 12.6% at one year, but for demented patients six times higher at

30- and 90-days, and 3.5 times at one year. The highest impact of cognitive impairment was seen during the first three months. This observation confirms the results from other studies [14,35,37] and may - at least partly - be explained by the rehabilitation difficulties in patients with cognitive impairment.[38] We were surprised to find a 2–3 times enhanced mortality in the subgroup with MCI (CDR:0.5), reflecting a level of cognitive impairment, which generally remains unnoticed in the social context. This observation highlights even more the importance of assessing cognitive function in patients with AHF.

For the most common form of dementia, AD, analysing biomarkers could state more precisely, if a CDR:0 corresponds to a pre-AD condition or simply a mental decline by age. However, altered concentrations of biomarkers can be seen in early stages of AD – and like Aβ42 – even years before diagnosis.[23,24] This might explain the results noted in subgroup B-patients, where the trauma *per se* could have accelerated the development of cognitive symptoms, enhancing mortality. We examined in our cohort, if these markers' concentrations were related to dementia by itself, thus being a surrogate marker of this phenomenon (*i.e. AD*), and if these concentrations could serve as predictor for mortality after AHF surgery. We found positive associations between decreased Aβ42/Aβ40 as well as increased T-tau concentrations and postoperative 90- and 365-day mortality. These altered concentrations are similar to those found in AD.[20,39]

At 30 days, however, biomarkers were not related to mortality. This was not surprising, as age, comorbidities, and peri-operative care probably influence early mortality more than cognitive impairment *per se*.

Mortality increased with higher T-tau- and lower Aβ42/Aβ40-levels. In this study, we could not discriminate for the individual patient, if the increase of T-tau, a biomarker for brain injury,[40] was due to dementia or an eventual head trauma associated to the AHF. Therefore, we focused only on Aβ42/Aβ40-levels, when investigating 4 subgroups (table 6). Here, cognitively intact patients without altered AD-biomarkers (subgroup A) had considerably lower mortality than cognitively impaired patients with altered AD-biomarkers (D), confirming previous results from retrospective studies.[7,14] Our results in the intermediary groups (B and C) were especially interesting, where cognitively intact patients with abnormal AD-biomarkers (group B) had a threefold higher mortality at 90 days, than those with normal AD-biomarkers (A). Although this difference was not significant, it might indicate an accelerated cognitive decline, like pre-AD, after the hip trauma. That makes these patients more vulnerable in the rehabilitation phase and could explain the poor outcome. We believe that this emphasizes the importance of analysing biomarkers, as they may reveal a difference in prognosis in these cognitively intact patients at admission. We also found a high

mortality in group C (cognitive impairment and normal AD-biomarkers) at all investigated time-points. This group might represent other types of dementia, which are not captured by the tested AD-biomarkers, but indicates that cognitive impairment *per se*, independent of origin, enhances mortality.

Our results demonstrate that mortality is significantly higher in demented patients, and particularly in those with biochemical evidence for AD. These results are still significant when adjusted for age. Surprisingly, even in patients with preclinical AD, (confirmed by a normal CDR-score in combination with positive biomarkers), a higher absolute level of mortality is noted after AHF surgery.
The question is, how to recognize those patients in time, to improve their outcome.
To measure tau in blood samples is already possible and probably even the Aβ42/Aβ40-ratio in the near future. Thus, geriatricians, anaesthesiologists, or orthopaedic surgeons may pre-operatively be able to evaluate the mortality- and morbidity-risk for AHF-patients with a combined evaluation of dementia coupled to biomarker concentrations.

A limitation of our study is that we investigated different degrees of dementia, but not the rate and extent of delirium, which is a common condition seen in elder patients with AHF. Distinction between dementia and delirium can be difficult in the preoperative setting. To omit this uncertainty in the present study, we contacted next-of-kin of all patients that were not mentally intact. This allowed us to evaluate the patient's cognitive status of the period immediately prior to the hip trauma. Thereby we captured all patients that had dementia pre-trauma and could probably exclude delirium as cause of high pre-operative CDR-scores. But our results could be influenced by peri-operative delirium, which we did not examine. Another limitation is the absence of a control group in our study, and we only refer to the standardized mortality ratio in Sweden to assume the mortality risk for all patients of the same age- and gender. We collected registered dates of death, but not their official causes, which most often are multifactorial and related to advanced age and comorbidities. Further, we did not investigate the impact of different surgical therapies (and types of osteosynthesis) for AHF on mortality, which may have effected mortality during the first 30 days. Future prospective studies will reveal whether the choice of surgical procedure may have a special impact on demented patients.

CONCLUSION

We corroborate that individuals with cognitive impairment have a higher risk of mortality following an acute hip fracture. We extend this result by showing that there is an association of biomarker

evidence of AD pathology and mortality, and that this association might be present also in individuals in pre-dementia stages of the disease.

The CSF levels of the biomarkers T-tau and the ratio Aβ42/Aβ40 may be used to enhance the accuracy of risk scoring models for predicting mortality in patients with AHF.

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TABLES AND FIGURES

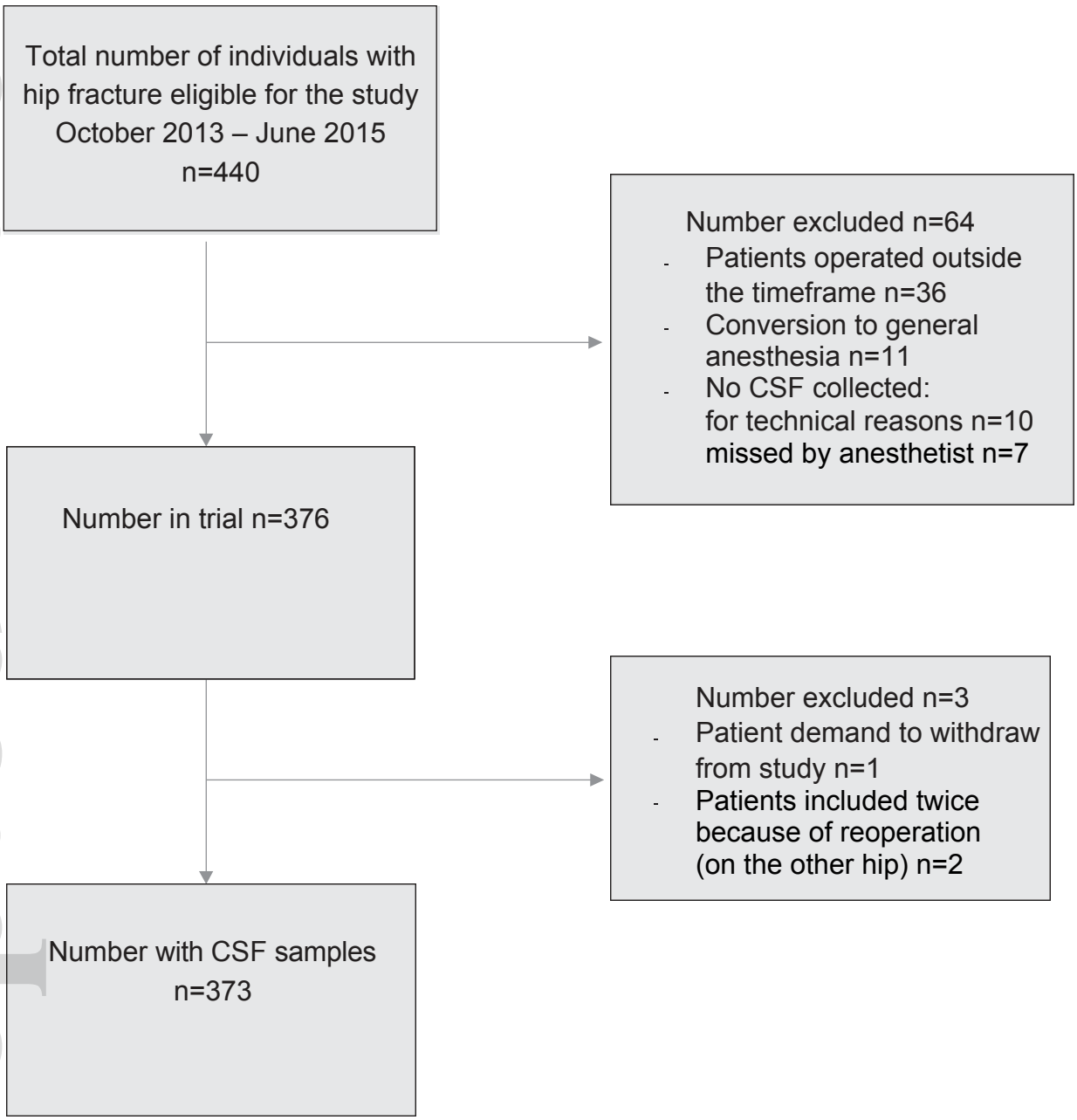

Figure 1. Flowchart: Enrollment of patients in the study

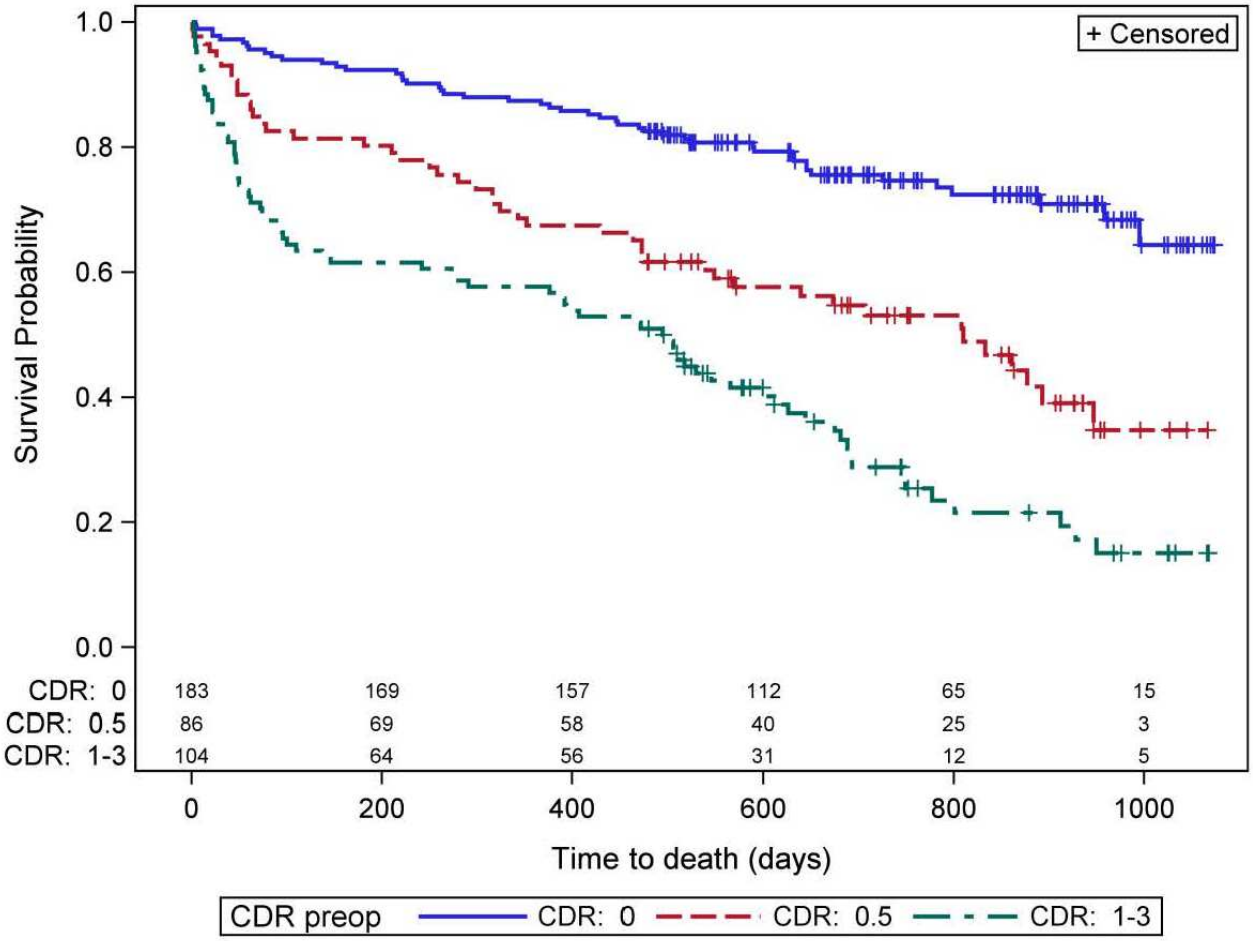

Figure 2. Survival from date of surgery related to CDR.

Kaplan Meier Plot with study-population n=373: Time of survival after surgery related to the degree of cognitive impairment, expressed by the Clinical Dementia Rating (CDR), divided in 3 groups: CDR:0, CDR:0.5, and CDR:1–3. Time is indicated by days. Survival probability is indicated as a fraction of surviving patients (with indication of the number of patients still included after censoring at 30 October 2016)

Table 1. Baseline table

Variable	Total patient cohort (n=373)	Group I CDR=0 (n=183)	Group II CDR=0.5 (n=86)	Group III CDR=1–3 (n=104)	*p-value*
Gender					
Male	98 (26.3%)	57 (31.1%)	21 (24.4%)	20 (19.2%)	
Female	275 (73.7%)	126 (68.9%)	65 (75.6%)	84 (80.8%)	*0.025*
Age (years)	83.4 (+/-10.2) 86.0 (44 – 102)	79.3 (+/-11.0) 82.0 (44 – 100)	86.4 (+/-8.5) 88.0 (56 – 102)	88.2 (+/-6.4) 89.0 (68 – 102)	*<.0001*
Height (m)	1.67 (+/-0.09) 1.65 (1.47 – 1.99)	1.68 (+/-0.09) 1.67 (1.47 – 1.99)	1.67 (+/-0.09) 1.65 (1.50 – 1.90)	1.64 (+/-0.07) 1.65 (1.50 – 1.90)	*0.0069*
Weight (kg)	64.3 (+/-12.8) 63.0 (36.0 – 115.0)	65.6 (+/-13.4) 65.0 (36.0 – 105.0)	64.6 (+/-13.4) 63.2 (40.0 – 115.0)	61.5 (+/-10.8) 60.0 (36.5 – 90.0)	*0.065*
BMI	23.0 (+/-3.5) 22.9 (12.6 – 34.9)	23.1 (+/-3.6) 23.2 (12.6 – 34.1)	22.9 (+/-3.6) 22.8 (14.0 – 34.9)	22.8 (+/-3.4) 22.1 (14.3 – 33.1)	*0.50*
ASA					
1	17 (4.6%)	16 (8.7%)	1 (1.2%)	0 (0.0%)	
2	181 (48.5%)	101 (55.2%)	40 (46.5%)	40 (38.5%)	
3	160 (42.9%)	61 (33.3%)	42 (48.8%)	57 (54.8%)	
4	15 (4.0%)	5 (2.7%)	3 (3.5%)	7 (6.7%)	*<.0001*
ASA (medium/ median)	2.5 2.0 (1 – 4)	2.3 2.0 (1 – 4)	2.5 3.0 (1 – 4)	2.7 3.0 (2 – 4)	

Nottingham hip fracture score (NHFS)					
0	5 (1.3%)	5 (2.7%)	0 (0.0%)	0 (0.0%)	
1	11 (2.9%)	11 (6.0%)	0 (0.0%)	0 (0.0%)	
2	5 (1.3%)	5 (2.7%)	0 (0.0%)	0 (0.0%)	
3	52 (13.9%)	41 (22.4%)	11 (12.8%)	0 (0.0%)	
4	86 (23.1%)	58 (31.7%)	26 (30.2%)	2 (1.9%)	
5	79 (21.2%)	35 (19.1%)	29 (33.7%)	15 (14.4%)	
6	67 (18.0%)	22 (12.0%)	10 (11.6%)	35 (33.7%)	
7	51 (13.7%)	6 (3.3%)	10 (11.6%)	35 (33.7%)	
8	15 (4.0%)	0 (0.0%)	0 (0.0%)	15 (14.4%)	
9	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (1.9%)	*<.0001*
NHFS (medium/ median)	4.9 (+/-1.7) 5.0 (0 – 9)	4.0 (+/-1.5) 4.0 (0 – 7)	4.8 (+/-1.2) 5.0 (3 – 7)	6.5 (+/-1.0) 6.5 (4 – 9)	*<.0001*
Comorbidities					
COPD	39 (10.5%)	22 (12.0%)	8 (9.3%)	9 (8.7%)	*0.35*
Earlier stroke	70 (18.8%)	23 (12.6%)	18 (20.9%)	29 (27.9%)	*0.0012*
Memory disorders	147 (39.4%)	8 (4.4%)	40 (46.5%)	99 (95.2%)	*<.0001*
Parkinson's disease	8 (2.1%)	2 (1.1%)	2 (2.3%)	4 (3.8%)	*0.12*
Depression	62 (16.6%)	15 (8.2%)	17 (19.8%)	30 (28.8%)	*<.0001*
Heart insufficiency	36 (9.7%)	16 (8.7%)	12 (14.0%)	8 (7.7%)	*0.94*
Hypertension	198 (53.1%)	92 (50.3%)	48 (55.8%)	58 (55.8%)	*0.33*

Diabetes mellitus	52 (13.9%)	27 (14.8%)	12 (14.0%)	13 (12.5%)	*0.60*
Renal insufficiency	40 (10.7%)	18 (9.8%)	12 (14.0%)	10 (9.6%)	*0.93*
CDR					
0	183 (49.1%)	183 (100.0%)	0 (0.0%)	0 (0.0%)	
0.5	86 (23.1%)	0 (0.0%)	86 (100.0%)	0 (0.0%)	
1	25 (6.7%)	0 (0.0%)	0 (0.0%)	25 (24.0%)	
2	36 (9.7%)	0 (0.0%)	0 (0.0%)	36 (34.6%)	
3	43 (11.5%)	0 (0.0%)	0 (0.0%)	43 (41.3%)	

Baseline data for patients enrolled in the study:

For categorical variables: n and (%) is presented.

For continuous variables: mean (+/- SD) / median (min – max) is presented.

For comparison between groups the Mantel-Haenszel Chi Square test was used for ordered categorical variables and the Kruskal-Wallis test for continuous variables.

Table 2. Standardized mortality ratio (SMR)

Study population compared to population in Sweden

Label	Number of observations	Observed person years	Observed events	Expected events	SMR value	95% CI	*p-value*
All subjects	373	578	170	65.5	2.6	2.2–3.0	*<0.0001*
CDR: 0	183	334	48	28.3	1.7	1.3 - 2.2	*0.0009*
CDR: 0.5	86	129	46	19.5	2.4	1.7 - 3.2	*<0.0001*
CDR: 1-3	104	116	76	17.7	4.3	3.4 - 5.4	*<0.0001*

Table 3. CDR and mortality

Subgroup			Dead at 30 days			Dead at 90 days			Dead at 365 days		
Group	CDR	n	n (%) of events	OR (95%CI)	*p*-value	n (%) of events	OR (95%CI)	*p*-value	n (%) of events	OR (95%CI)	*p*-value
I	0	183	5 (2.7%)	2.70 (1.62-4.50)	*0.0001**	10 (5.5%)	2.75 (1.92-3.94)	*<0.0001**	23 (12.6%)	2.23 (1.68-2.97)	*<0.0001**
II	0.5	86	5 (5.8%)			15 (17.4%)			28 (32.6%)		
III	1-3	104	17 (16.3%)			33 (31.7%)			44 (42.3%)		
Adjusted for age				2.15 (1.26-3.69)	*0.0053**		2.19 (1.49-3.20)	*<0.0001**		1.78 (1.32-2.42)	*0.0002**
Entire cohort		373	27 (7.2%)			58 (15.5%)			95 (25.5%)		

The table shows the mortality rates at 30, 90, and 365 days post–surgery for patients with AHF presenting different degrees of cognitive impairment at admission to
the hospital: CDR 0, CDR 0.5, and CDR 0-3.
OR is the ratio for the odds for an increase of the predictor of a defined unit, referring to group I (CDR 0).
p-values and OR are based on original values and not on stratified groups.
All tests are performed with univariate logistic regression, and adjusted for age using logistic regression.

CI = Confidence Interval. *significant *p*-value.

Table 4. Descriptive table of selected variables between patients alive/dead at 30 days, 3 months and 1 year

Variable	at 30 days		at 90 days		at 365 days	
	Alive (n=346)	Dead (n=27)	Alive (n=314)	Dead (n=58)	Alive (n=277)	Dead (n=95)
Sex: M	88 (25.4%)	10 (37.0%)	82 (26.0%)	16 (27.6%)	70 (25.2%)	28 (29.5%)
Sex: F	258 (74.6%)	17 (63.0%)	233 (74.0%)	42 (72.4%)	208 (74.8%)	67 (70.5%)
Age (years)	82.9 (+/-10.3)	90.1 (+/-5.3)	82.3 (+/-10.3)	89.7 (+/-6.7)	81.7 (+/-10.4)	88.5 (+/-7.5)
	85 (44–102)	90 (79–102)	84 (44–102)	90 (69–102)	84 (44–100)	90 (69–102)
Aβ42	343 (+/-181)	308 (+/-129)	350 (+/-183)	288 (+/-140)	350 (+/-183)	310 (+/-158)
(pg/ml)	298 (58–1229)	289 (128–625)	310 (58–1229)	244 (74–749)	307 (58–1229)	278 (74–905)
Aβ42/Aβ40-	0.63 (+/-0.22)	0.61 (+/-0.25)	0.64 (+/-0.22)	0.57 (+/-0.22)	0.64 (+/-0.22)	0.60 (+/-0.23)
ratio x 10	0.58 (0.28–1.11)	0.50 (0.30–1.03)	0.60 (0.28–1.11)	0.49 (0.30–1.03)	0.60 (0.28–1.11)	0.50 (0.30–1.06)
T-tau	413 (+/-228)	497 (+/-222)	402 (+/-227)	507 (+/-220)	400 (+/-225)	475 (+/-232)
(pg/ml)	355 (47.5–1812)	401 (194–997)	346 (47.5–1812)	446 (145–1024)	345 (53.7–1812)	419 (47.5–1381)
p-tau	58.6 (+/-27.5)	62.3 (+/-27.9)	58.3 (+/-27.3)	62.1 (+/-28.4)	58.5 (+/-28.1)	59.9 (+/-25.8)
(pg/ml)	52 (16–168)	51 (26–151)	52 (16–168)	53 (17–155)	52 (16–168)	54 (16–155)

Variables presented are: Sex, Age, Biomarkers Aβ42, T-tau, p-tau and the ratio (Aβ42/Aβ40) x10.

For categorical variables n (%) is presented.

For continuous variables Mean (+/-SD) / Median (min – max) is presented.

Table 5. Neuromarkers and mortality at 30, 90 and 365 days

Variable	range	30-day mortality n (%) of events	30-day mortality OR (95%CI)	30-day mortality *p-value*	90-day mortality n (%) of events	90-day mortality OR (95%CI)	90-day mortality *p-value*	365-day mortality n (%) of events	365-day mortality OR (95%CI)	365-day mortality *p-value*
Aβ42 (pg/mL)	58–211	6 (6.5%)			19 (20.4%)			30 (32.3%)		
(OR per 100 units)	212–297	8 (8.6%)	0.88 (0.69-1.14)	*0.33*	17 (18.3%)	0.79 (0.65–0.96)	*0.017**	24 (25.8%)	0.87 (0.75-1.01)	*0.061*
	298–419	8 (8.5%)			14 (14.9%)			21 (22.3%)		
	420–1229	5 (5.4%)			8 (8.6%)			20 (21.5%)		
Ratio Aβ42/Aβ40	0.28–0.42	8 (8.6%)			22 (23.7%)			29 (31.2%)		
(OR per 0.1 units)	0.43–0.57	8 (8.6%)	0.95 (0.79-1.14)	*0.57*	17 (18.3%)	0.85 (0.74–0.97)	*0.017**	30 (32.3%)	0.91 (0.82-1.01)	*0.087*
	0.58–0.82	3 (3.2%)			7 (7.4%)			11 (11.7%)		
	0.83–1.11	8 (8.6%)			12 (12.9%)			25 (26.9%)		

Ratio Aβ42/Aβ40 (abnormal/normal)	≤0.64	18 (8.6%)	0.62 (0.27-1.43)	*0.26*	41 (19.5%)	0.48 (0.26–0.88)	*0.018**	62 (29.5%)	0.61 (0.37-0.98)	*0.042**
	>0.64	9 (5.5%)			17 (10.4%)			33 (20.2%)		
T-tau (pg/mL) (OR per 100 units)	47–265	2 (2.5%)	1.14 (0.97-1.33)	*0.11*	5 (6.3%)	1.19 (1.06–1.33)	*0.004**	12 (15.2%)	1.14 (1.03-1.27)	*0.014**
	266–362	4 (5.1%)			10 (12.7%)			17 (21.5%)		
	363–515	8 (10.0%)			16 (20.0%)			24 (30.0%)		
	516–1812	7 (8.9%)			19 (24.1%)			27 (34.2%)		
P-tau (pg/mL) (OR per 10 units)	16–40	3 (3.1%)	1.05 (0.92-1.20)	*0.51*	10 (10.4%)	1.05 (0.95–1.16)	*0.33*	20 (20.8%)	1.02 (0.94-1.11)	*0.67*
	41–51	11 (13.1%)			15 (17.9%)			22 (26.2%)		
	52–70	6 (6.1%)			18 (18.4%)			27 (27.6%)		
	71–168	7 (7.4%)			15 (16.0%)			26 (27.7%)		

The table shows the mortality rates at 30, 90 and 365 days post–surgery for patients presenting concentrations of biochemical neuromarkers in different ranges, with a total of 27, 58 resp. 95 lethal events (except T-tau: total 21, 50 resp. 80 for 317 obtained analyses).

Variables presented are: Biochemical neuromarkers Aβ42, T-tau, P-tau and the ratio Aβ42/Aβ40 x 10.

The ratio Aβ42/Aβ40 x 10 is shown in 4 quartiles and in a modified analysis with normal vs. pathological values (cut-off: 0.64).

OR is the ratio for the odds for an increase of the predictor of a defined unit. p-values and OR are based on original values and not on stratified groups.

All tests are performed with univariate logistic regression. CI = Confidence Interval. *significant *p*-value.

Table 6. Mortality rates for subgroups

a) Observed mortality for subgroups

Subgroup					Observed mortality at					
	Cognitive function	Aβ42/Aβ40-ratio	n		30 days		90 days		365 days	
A	normal	normal	183	102	5 (2.7%)	2 (1.9%)	10 (5.5%)	3 (2.9%)	23 (12.6%)	12 (11.8%)
B		abnormal		81		3 (3.7%)		7 (8.6%)		11 (13.6%)
C	abnormal	normal	190	61	22 (11.6%)	7 (11.5%)	48 (25.3%)	14 (23.0%)	72 (37.9%)	21 (34.4%)
D		abnormal		129		15 (11.6%)		34 (26.4%)		51 (40.0%)
All patients in entire study				373	27 (7.2%)		58 (15.5%)		95 (25.4%)	

b) Univariate logistic regression for subgroups. Dependent: Death within defined time

Subgroup				Odds ratio for death at					
				30 days		90 days		365 days	
	Cognitive function	Aβ42/Aβ40-ratio	n	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
A	normal	normal	102	1.0		1.0		1.0	
B		abnormal	81	1.9 (0.3-12)	*0.48*	3.1 (0.8-12)	*0.11*	1.2 (0.5-2.8)	*0.71*

C	abnormal	normal	61	6.5 (1.3-32)	*0.023**	9.8 (2.7-36)	*0.0005**	3.9 (1.8-8.8)	*0.0008**
D		abnormal	129	6.6 (1.5-29)	*0.014**	11.8 (3.5-40)	*<0.0001**	4.9 (2.4-9.7)	*<0.0001**

c) Univariate logistic regression for subgroups adjusted for age. Dependent: Death within defined time

Subgroup				Odds ratio for death at					
				30 days		90 days		365 days	
	Cognitive function	Aβ42/Aβ40-ratio	n	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
A	normal	normal	102	1.0		1.0		1.0	
B		abnormal	81	1.6 (0.3-10)	*0.60*	2.7 (0.7-11)	*0.11*	1.0 (0.4-2.5)	*0.71*
C	abnormal	normal	61	4.5 (0.9-23)	*0.07*	7.1 (1.9-27)	*0.004**	2.9 (1.3-6.7)	*0.01**
D		abnormal	129	3.3 (0.7-15)	*0.13*	6.2 (1.8-22)	*0.004**	2.7 (1.3-5.8)	*0.008**

The tables show the mortality rate at 30, 90 and 365 days *vs.* subgroups.

Definition of subgroups. Cognitive normal: CDR=0, abnormal: CDR≥0.5 Biomarker normal: Aβ42/Aβ40-ratio > 0.064;

Biomarker abnormal: Aβ42/Aβ40-ratio ≤ 0.064

Presented in (a): number of patients (n) and % of lethal events in each group. Presented in (b and c): OR and p-values.

OR is the ratio for the odds for an increase of the predictor of a defined unit, with 95% CI = 95% Confidence interval.

*significant p-value.