Frailty Index and incident mortality, hospitalization and institutionalization in Alzheimer's disease: data from the ICTUS study

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Running head: Frailty Index and adverse health outcomes in AD patients

Abstract

BACKGROUND: The identification of an objective evaluation of frailty capable of predicting adverse outcomes in Alzheimer's disease (AD) is increasingly discussed. The purpose of this study was to investigate whether the Frailty Index (FI) predicts hospitalization, institutionalization and mortality in AD patients.

METHODS: Prospective multicenter cohort study (follow-up=2 years), including 1,191 subjects with AD. The outcomes of interest were incident hospitalization, institutionalization, and mortality. The FI was calculated as the ratio of actual to thirty potential deficits, i.e. deficits presented by the participant divided by 30. Severity of dementia was assessed using the Clinical Dementia Rating (CDR) score. Cox proportional hazard models were performed.

RESULTS: Mean age of the study sample was 76.2 (standard deviation=7.6) years old. A quadratic relationship of the FI with age was reported at baseline (R^2=0.045, p<0.001). The FI showed a statistically significant association with mortality (age- and gender-adjusted HR=1.019, 95%CI=1.002-1.037, p=0.031) and hospitalization (age- and gender-adjusted HR=1.017, 95%CI=1.006-1.029, p=0.004), and a borderline significance with institutionalization. When the CDR score was simultaneously included in the age- and gender-adjusted models, the FI confirmed its predictive capacity for hospitalization (HR=1.019, 95%CI=1.006-1.032, p=0.004), whereas the CDR score was the strongest predictor for mortality (HR=1.922, 95%CI=1.256-2.941, p=0.003) and institutionalization (HR=1.955, 95%CI=1.427-2.679, p<0.001).

CONCLUSIONS: The FI is a robust predictor of adverse outcomes even after the stage of the underlying dementia is considered. Future work should evaluate the clinical implementation of the FI in the assessment of demented individuals in order to improve the personalization of care.

Keywords: Frailty, Frailty Index, Alzheimer's disease, dementia, cognition, mortality, institutionalization, hospitalization

Background

Population aging is leading to a considerable increase of age-related detrimental conditions, such as dependence and disability[1]. In this context, frailty has attracted a significant and increasing scientific interest[2], because it is considered as a promising opportunity to quit the obsolete chronological criterion of age in the clinical decision process.

Frailty is a multidimensional syndrome characterized by decreased reserves and diminished resistance to stressors due to the cumulative declines of multiple physiological systems[3, 4]. Among the most commonly used operational definitions of frailty, the model proposed by Rockwood and colleagues (the so-called "Frailty Index", FI)[5].

The FI is founded on the theoretical concept that frailty is resulting from the arithmetical accumulation of deficits occurring with aging. Its operationalization takes into account clinical signs, symptoms, diseases, disabilities, psychosocial risk factors, and geriatric syndromes, resulting in a score which has shown to be strongly associated with negative health-related outcomes (e.g., hospitalization, institutionalization, and death) in community-dwelling older persons[6].

The FI has been indicated as a marker of biological aging. Moreover, its internal structure allows a better discrimination of the risk because resembling a continuous variable [7]. This implies that the FI is more sensible than other instruments at perceiving subtle variations of the health status. In other words, it allows to differentiate individuals in a more subtle way and substantially reduce the risk of possible ceiling/floor effects in the assessment of populations[7].

Accumulating evidence supports an independent association between frailty and dementia[8, 9]. Moreover, a large body of literature shows the individual association of both frailty and dementia to adverse health-related outcomes in population studies[10-13]. However, to

our knowledge, there are currently no population studies examining whether frailty (intended as resulting from the age-related accumulation of deficits) may predict hospitalization, institutionalization and mortality in patients with Alzheimer's disease (AD). We hypothesize that the FI (i.e., an objective measure of deficits accumulation closely reflecting the biological status of individuals) may provide a better estimate of the vulnerability status compared to measures assessing the severity of dementia (such as the Clinical Dementia Rating [CDR] score[14]) in this population. In fact, the FI may improve the discrimination of risk for negative outcomes among patients with same chronological age and similar stage of dementia. The differentiation of risk profile in complex populations (such as the one composed by AD patients) is crucial in order to design and implement personalized interventions.

Thus, the primary aim of the present study was to examine whether the FI predicts incident hospitalizations, institutionalization, and mortality in a large sample of AD patients. The secondary aim was to simultaneously test the capacity of the FI and the severity of dementia (assessed by the Clinical Dementia Rating [CDR] score) in the prediction of negative health-related events in AD.

Methods

Participants and study design

Data are from the Impact of Cholinergic Treatment USe (ICTUS) study, which has been previously described elsewhere[15]. Briefly, the ICTUS study is a prospective multicenter cohort study aimed at evaluating the clinical course, treatment outcomes, and socioeconomic impact of AD in Europe. It involved 29 participating centers from 12 European countries, all members of the European Alzheimer Disease Consortium (EADC), a network of clinical and research institutions specialized in the diagnosis and treatment of AD.

The inclusion of participants in ICTUS was based on the following criteria: 1) diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria; 2) MMSE score ranging from 10 to 26[16]; 3) living in the community with a well-identified informal caregiver; 4) absence of known conditions reducing to less than 2 years the patient's life expectancy; 5) ability to sign an informed consent.

The study was approved by the Ethics Committee of the Toulouse University Hospital (coordinating center) and at individual centers by local or national ethical committees. All the study participants signed informed consent.

Overall, a total of 1,375 patients were recruited in the ICTUS study. After the baseline assessment (conducted between February 2003 and July 2005), participants were followed up over 2 years with mid-term re-evaluations every 6 months. At baseline and each follow-up visit, a comprehensive clinical and neuropsychological assessment was performed.

The present analyses were performed in 1,191 subjects after exclusion of 184 subjects having missing values for the outcomes and/or the predictor of interest. Participants excluded

from the present analyses tended to be frailer and present more outcomes than those included in the analytical sample.

Outcomes

In the present study, the outcomes of interest were incident hospitalization, institutionalization, and mortality. Data on the three outcomes were self-reported provided by the caregiver and collected at each 6 month visit in the study center.

The institutionalization (in any long-term care facility) and mortality outcomes were assessed considering the entire two-year period of follow-up in order to maximize the number of events. Differently, the definition of incident hospitalization events was censored to the first year of follow-up in order to better render the FI closer to the participant's clinical status and avoid the inference of unforeseeable (and clinically unrelated) events (potentially justifying a long-term hospitalization). It is also worth to be mentioned that the exploration of short-term hospitalizations may provide a stronger clinical relevance to the study results because more directly affecting the immediate planning of interventions following an eventual FI assessment. This approach was previously used in the literature when exploring such heterogeneous outcome[17, 18].

Independent variable of interest

The FI was generated taking advantage of the ICTUS data coming from the comprehensive assessment of the participants' health status performed at the baseline visit. Overall, 30 variables were included in the construction of the FI (**Table 1**). All the items considered for computing the FI were coded as dichotomous variables, where a value of 0 indicates the absence of the deficit and a value of 1 its presence. The FI was computed by calculating the ratio between the number of deficits presented by the participant and the total

number of considered items (i.e., 30). Therefore, the FI can range from a score of 0 (no deficit is present) to 1 (all deficits are present). It has been previously reported that an index composed by a minimum of 30 variables is sufficiently robust to ensure an accurate computation of the subject's deficit accumulation[19, 20]. Although the FI was designed to be used as a continuous variable, it has sometimes been categorized for providing it more clinical relevance. In the present analyses, results are provided for the FI as a continuous variable as well as after its categorization (using the previously adopted 0.25 cut-point)[21].

In the present study, secondary analyses were specifically aimed at comparing the predictive capacity of the FI when the stage of dementia is simultaneously taken into account. In this context, the CDR score assessed at the baseline visit was used to measure the severity of dementia. The CDR scale is an instrument measuring the residual functional capacities of the individual in relationship with his/her cognitive abilities along five levels of impairment (rated as 0, 0.5, 1, 2 or 3). The rating is generated by the evaluation of six different domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Global CDR calculated using the algorithm proposed by Morris[14] ranges from 0 (no dementia) to 3 (severe dementia). None of the patients in the ICTUS study presented a CDR score equal to 0 due to the eligibility criteria applied to the enrollment of participants.

Other variables

Socio-demographic information (age, gender, education), clinical factors (self-reported diagnosis of diabetes, hypertension, ischemic heart disease, stroke, and seizures), and cognitive and functional data recorded at the baseline assessment were used for describing the study sample.

Statistical analysis

The relationship between the FI and age was first tested using the curve estimation option in SPSS to obtain a regression plot and estimated R squared (R^2) value at baseline. Cox proportional hazard models were performed to study the relationship between the FI (both as continuous and categorical variable) with the outcomes of interest. Results are presented as hazard ratios (HR) and 95% confidence intervals (95%CI). The time variable for the subjects who died was censored at the date of death. For the subjects that were hospitalized the time variable was censored at the date of the first event occurred during the follow-up. Similarly, for the subjects that were institutionalized, the time variable was censored at the date of entry in the long-term setting. For those who did not experience the studied outcomes, the time variable was censored at the last contact date.

In secondary analyses, Cox proportional hazard models were also performed to simultaneously test the FI and the CDR score in the prediction of the outcomes of interest. Survival curves for the relationship between the dichotomous variable of frailty were conducted for each of the three outcomes.

Statistical significance was set at a p value lower than 0.05. All statistical analyses were performed using SPSS statistical software version 18.0.0 (IBM Corp, New York).

Results

The main characteristics of the study sample (*n*=1,191) at the baseline assessment are presented in **Table 2**. Mean age of the population was 76.2 (standard deviation, SD=7.6) years. Women (63.8%) were more prevalent than men (36.2%). The mean FI was 0.21 (SD=0.12), ranging between 0 and 0.63. More than half of the sample (*n*=783, 65.7%) was not frail (FI<0.25), whereas 408 (34.3%) patients were frail (FI≥0.25). Among the 1,191 participants, 77 and 134 participants died and were institutionalized during the two-year follow-up, respectively. During the first year of follow-up, 185 incident hospitalization events were reported.

Figure 1 illustrates the quadratic relationship of the accumulation of deficits and age at baseline (R^2=0.045, *p*<0.001).

The survival curves for the relationship between the dichotomous FI variable and mortality and hospitalization, and institutionalization (p values for log rank <0.001, 0.003 and 0.010) are shown in **Figure 2 (Panels A, B, C)**, respectively.

The relationships of the FI with the studied outcomes are presented in **Table 3**. In both unadjusted and adjusted models, the FI showed a statistically significant association with mortality and hospitalization, and a borderline significance with institutionalization events. For example, considering that the FI (in percentage) is composed by 30 items, the presence of each additional deficit at the FI represents a >6% higher risk of mortality (HR 1.019), independently of age and gender. Consistently, frail individuals presented a higher risk for the three outcomes compared to non-frail.

Secondary analyses were also conducted to simultaneously test the FI and the CDR score (Spearman's *r*=0.4; *p*<0.001) in the prediction of the outcomes of interest (**Table 3**). In both the unadjusted and adjusted models, the severity of dementia was a stronger predictor of

mortality and institutionalization compared to the FI. In particular, after adjustment for age and gender, participants with higher CDR score presented an almost two-fold higher risk of mortality (HR=1.922, 95%CI=1.256-2.941, p=0.003) and institutionalization (HR=1.955, 95%CI=1.427-2.679, p<0.001), respectively. On the other hand, each additional deficit at the FI was significantly associated with about 6% higher risk of hospitalization (HR=1.019, 95%CI=1.006-1.032, p=0.004), independently of CDR.

Discussion

In the present study, we evaluated the predictive capacity of the FI on incident hospitalization, institutionalization, and mortality in a large cohort of AD patients. Our findings show that the FI significantly predicts mortality and hospitalization, and tends to predict institutionalization events in AD patients. To take these findings further, this study also explored which between the accumulation of deficits and the severity of dementia was more predictive of adverse health-related outcomes in this population. The accumulation of deficits was particularly predictive of hospitalization, even when the severity of dementia was simultaneously considered in the adjusted models. On the other hand, the CDR score seemed a better independent predictor of mortality and institutionalization than the FI.

Our results showed a quadratic relationship existing between age and FI. Such finding is consistent with previous studies conducted in different populations and settings[12, 22, 23], and extends the previous limited evidence existing for patients with AD[24]. Our findings confirm the robustness of this instrument for the identification of individuals at increased risk of adverse health-related outcomes. As previous studies demonstrated, the FI is strongly associated with hospitalization[25, 26], institutionalization[12, 27, 28] and mortality [11, 29-31] in different clinical settings. The FI may indeed represent a promising tool for following and monitoring the health (or vulnerability) modifications of the older persons also in patients with dementia. This is done by providing an objective assessment of their biological age (or frailty). In this context, it is noteworthy that the predictive value of the FI resides in its relative order rather than in its precise value. In fact, previous studies computing indexes focused on specific conditions and/or partial aspects of the individual's health status have still confirmed the predictive capacity of the approach when the relative weight (and not the absolute number) of the deficits was considered[32]. In our case, despite we might have missed some information

about the best deficits characterizing our sample, the predictive value of the relative model was not affected demonstrating its robustness.

In our analyses, when the severity of dementia (i.e., CDR score) was taken into account, the FI confirmed its predictive capacity for the hospitalization outcome. In contrast, the CDR score tended to be a stronger predictor of mortality and institutionalization than the FI. These findings might be explained by considering the FI as a stronger measure of the current biological status of the individual. Since it takes into account the accumulation of diseases, symptoms, disabilities, it might better capture outcomes that are more related to the clinical disruption of homeostasis (i.e., hospitalization). On the contrary, the severity of dementia may be a more "chronic" measure of the health status, reflecting the stage of the natural history of a specific condition (i.e., cognitive decline). Whereas it can provide an estimate of the length of disease (and, consequently, expected survival), it may not adequately perceive the heterogeneous modifications determining the frailty status. Consequently, the CDR score may show a stronger association than the FI with those outcomes particularly related to the duration of the disease (i.e., mortality and institutionalization in our case).

Although the theoretical basis of frailty is well established[3], its implementation (especially in the clinical practice) is still controversial. Between the two main operational models of frailty[7], the FI seems to have a greater discriminatory capacity due to its continuous and comprehensive nature compared to the categorical and physical domain-centered frailty phenotype proposed by Fried and colleagues [33, 34]. Although the frailty phenotype is composed by relatively easy-to-assess defining criteria, it is still unlikely that many individuals with dementia may complete it. For example, the cognitive impairment of the patient may limit his/her ability to adequately perform the physical function tests or provide reliable answers about signs and symptoms. Moreover, although the frailty phenotype is a useful screening tool for frailty, its use in the routine clinical practice, as outcome and as

target of interventions are strongly arguable. It is also noteworthy that the construct of the FI limits the floor or ceiling effects in extremely healthy or disabled populations, thus becoming applicable and meaningful across settings and populations. Differently from other frailty instruments, the FI is based on arithmetical assumptions which do not require the assessment of predefined criteria for measuring the frailty status. This implies that the FI (as in our case) can be generated *a posteriori* taking advantage of existing data collected for different purposes.

Our study has limitations worth to be described. As mentioned, the FI computed in ICTUS may miss some aspects of the participants' health status which might have been important to better refine the frailty assessment (e.g., impaired leisure activities, social issues). This limitation, reducing the comprehensive approach used in generation of the ICTUS FI, might explain the better performance of the CDR score for the mortality and institutionalization outcomes. Moreover, we could not conduct analyses explaining the causes of the studied events. It is possible that additional details about the causes of the studied outcomes would have provided different results. The translation of our findings in different settings (e.g., hospital, nursing homes) and populations (e.g., other than AD patients) should first be confirmed by *ad hoc* analyses.

In conclusion, the FI is a predictor of hospitalization, institutionalization and mortality in AD patients. The accumulation of deficits confirmed to be particularly associated with incident hospitalization events, independently of the stage of the underlying dementia condition. The need of adapting clinical care to the specific needs of the older patients requires instruments capable of perceiving the inner biological age of the individual. In this context, the FI may open interesting and promising scenarios in the field of neurodegenerative diseases, conditions that are particularly burdening for the person, their family, and public healthcare. The clinical implementation of the FI in the assessment of demented individuals

may improve the personalization of care by supporting the identification of an objective frailty status.

Competing interests: The authors declare that they have no competing interests.

Author's contributions: EK and CC performed the statistical analysis. EK and MC interpreted the data, and EK drafted the first version of the manuscript. SA and BV developed the concept, design and coordination of the original study. MC and EK further developed the hypothesis of the current manuscript. All authors revised critically the manuscript and approved the final manuscript.

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Figure 1. Frailty Index and age.

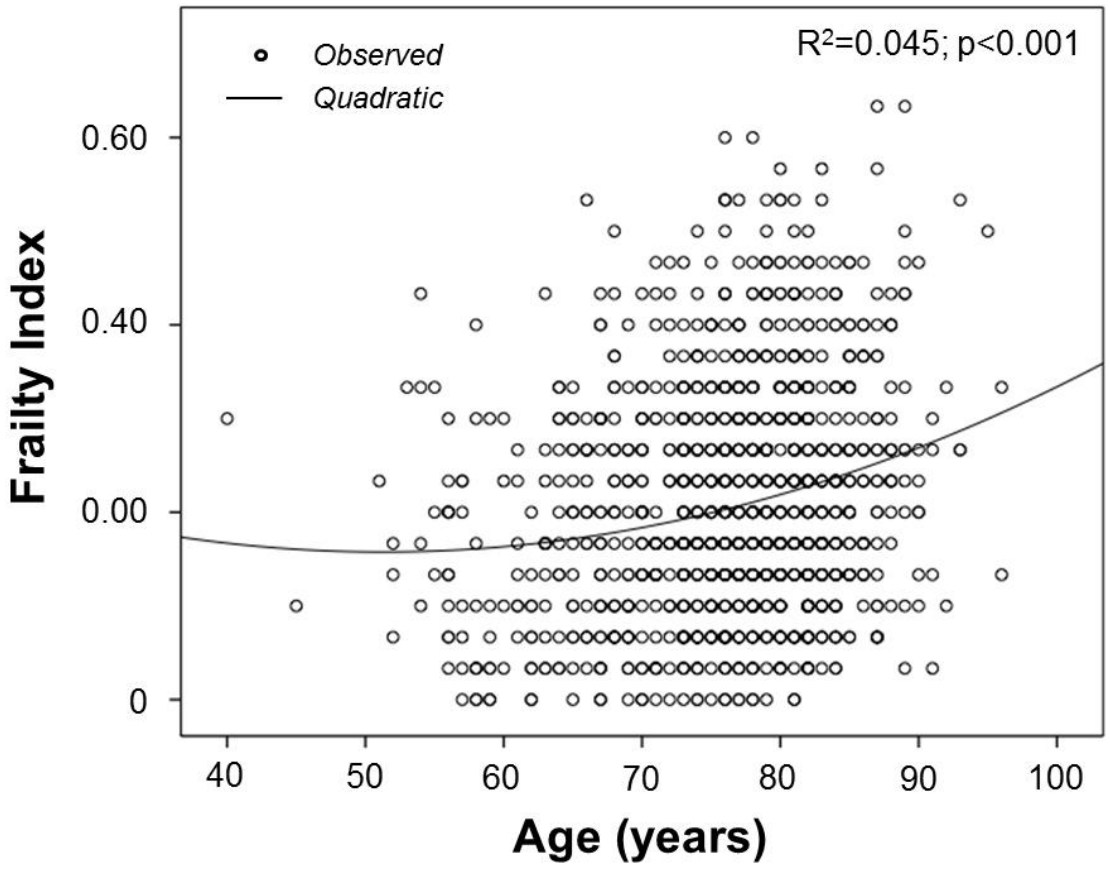
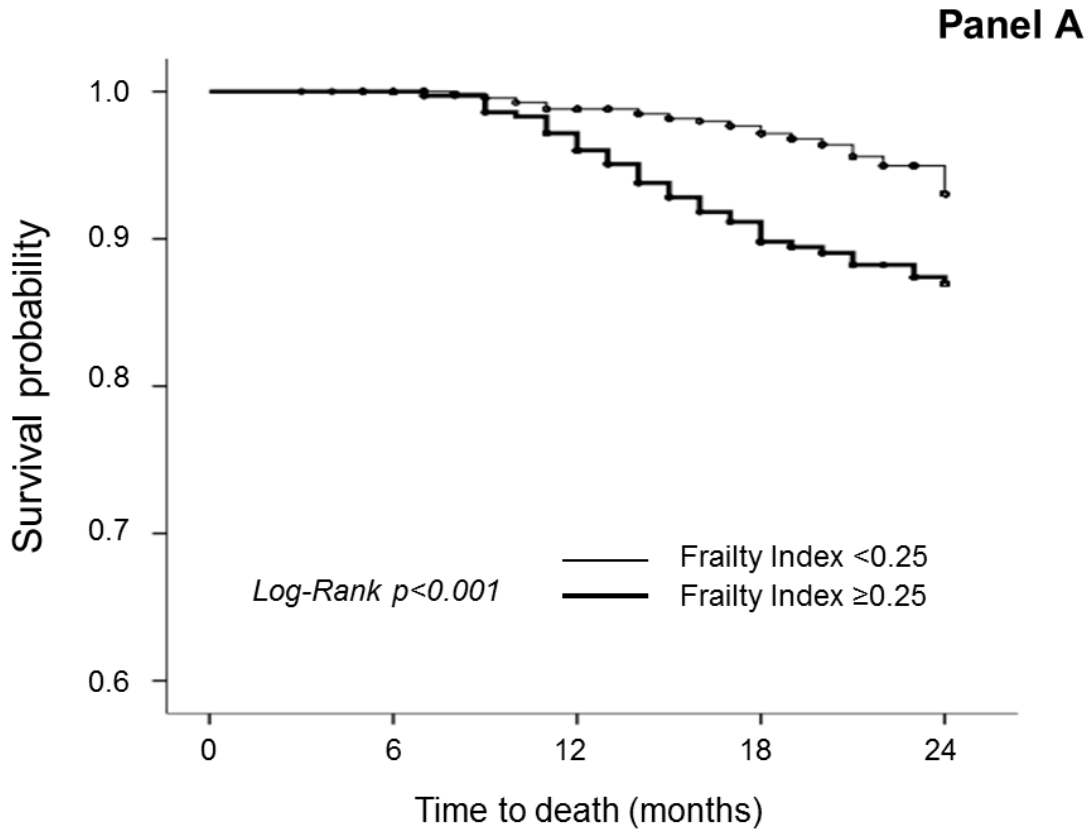
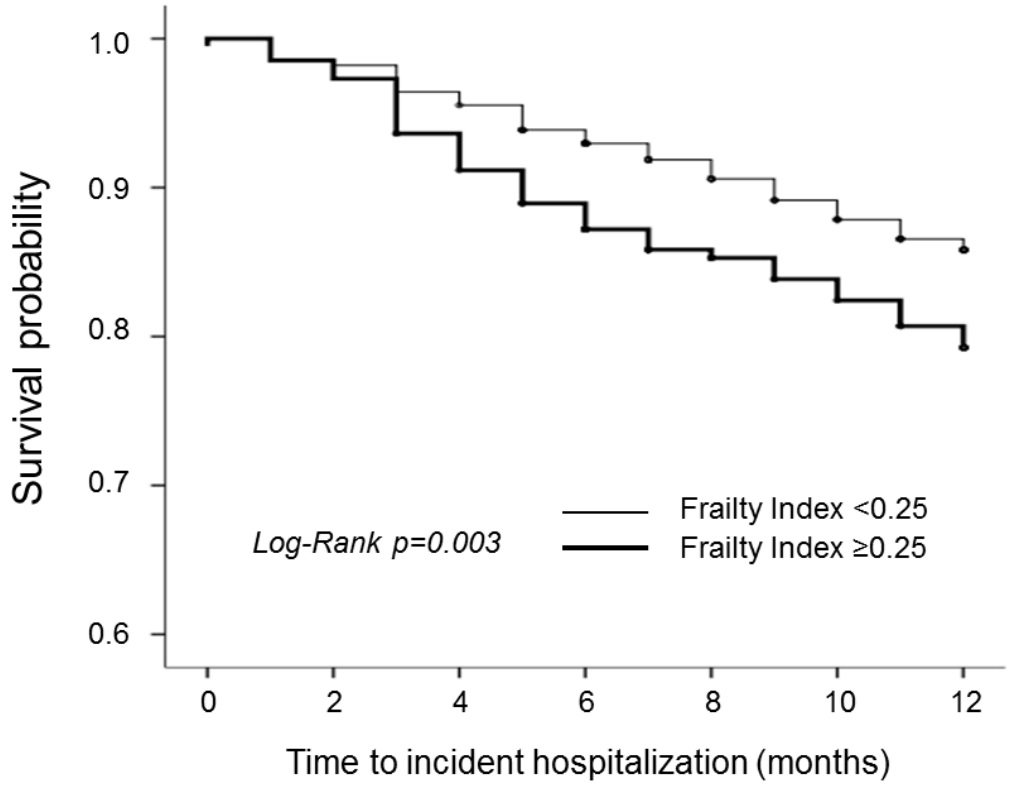


Figure 2. Survival curves of the Frailty Index categories with A) mortality, B) hospitalization and C) institutionalization. Bold and thin lines represent frail (Frailty Index ≥0.25) and non-frail (Frailty Index <0.25) participants, respectively.



Panel B


Survival probability
1.0
0.9
0.8
0.7
0.6
0
2
4
6
8
10
12
Time to incident hospitalization (months)
Log-Rank p=0.003
Frailty Index <0.25
Frailty Index ≥0.25

Panel C

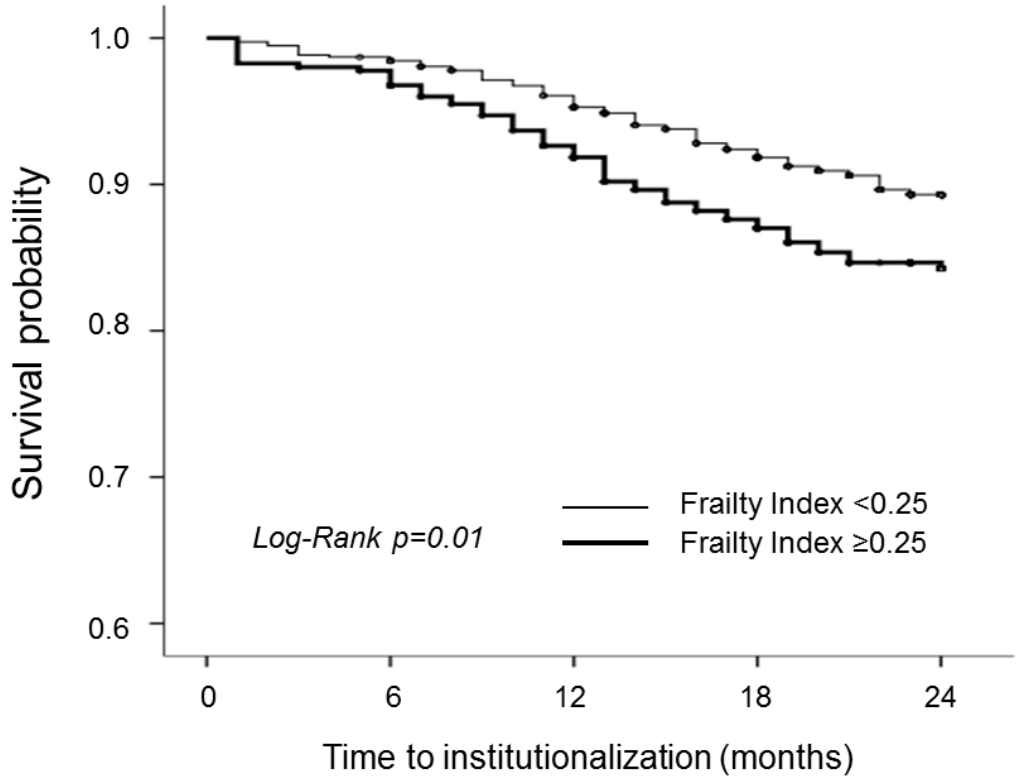

1.0
0.9
0.8
0.7
0.6
Survival probability
Log-Rank p=0.01
Frailty Index <0.25
Frailty Index ≥0.25
0
6
12
18
24
Time to institutionalization (months)

Table 1. Variables included in the Frailty Index (FI)

Diseases
Diabetes
Hypercholesterolemia
Hypertension
Ischemic heart disease
Depression
Stroke
Falls
Seizures
Parkinsonism
Focal signs
Disabilities
Help bathing
Help dressing
Help using toilet
Help getting in/out of chair
Incontinence
Help eating
Help taking medications
Symptoms
Delusions
Hallucinations
Agitation/aggression
Depression/dysphoria
Anxiety
Elation/euphoria
Apathy
Disinhibition
Irritability/lability
Aberrant motor behaviour
Sleep disorder
Appetite and eating disorders
Physical performance
Impaired one-leg stand test

Table 2. Baseline characteristics of the study sample (*n*=1,191)

	Mean (SD) or %
Age (years)	76.2±7.6
Gender (women)	63.8
Body mass index (kg/m^2)	25.2±4.2
Education (years)	8.0±4.7
Diabetes	11.6
Hypertension	39.0
Ischemic heart disease	13.2
Stroke	8.0
Falls	17.1
Seizures	1.1
Depression	24.5
ADAS-Cog (points)	20.5±9.2
MMSE (points)	20.6±3.9
CDR score (points)	
- 0.5	43.2
- 1	44.2
- ≥2	12.6
Frailty Index	0.21±0.12
ADL (/6)	5.5±0.9
IADL (/8)	4.9±2.2

Values are presented as means ± standard deviations (SD) or percentage

Table 3. Results from unadjusted and adjusted proportional hazard models testing the relationships of the FI (alone and simultaneously with the CDR score) for the mortality, hospitalization and institutionalization outcomes.

	Mortality	**P**	**Hospitalization**	**P**	**Institutionalization**	**P**
	n/N=77/1,191		n/N=185/1,191		n/N=134/1,191	
Unadjusted						
*Frailty Index (continuous)**	1.023 (1.005, 1.040)	0.011	1.018 (1.006, 1.030)	0.002	1.018 (1.004, 1.032)	0.009
Not frail (FI<0.25)	1		1		1	
Frail (FI≥0.25)	2.211 (1.413, 3.457)	0.001	1.557 (1.164, 2.083)	0.003	1.566 (1.112, 2.206)	0.010
*Frailty Index (continuous)**	1.009 (0.990, 1.028)	0.369	1.019 (1.006, 1.032)	0.003	1.003 (0.988, 1.019)	0.652
CDR score	2.038 (1.349, 3.081)	0.001	0.929 (0.679, 1.272)	0.648	2.028 (1.486, 2.766)	<0.001
Adjusted for age, gender						
*Frailty Index (continuous)**	1.019 (1.002, 1.037)	0.031	1.017 (1.006, 1.029)	0.004	1.011 (0.997, 1.025)	0.116
Not frail (FI<0.25)	1		1		1	
Frail (FI≥0.25)	1.409 (0.997, 1.992)	0.052	1.525 (1.137, 2.046)	0.005	2.121 (1.352, 3.325)	0.001
*Frailty Index (continuous)**	1.007 (0.987, 1.027)	0.494	1.019 (1.006, 1.032)	0.004	0.998 (0.983, 1.014)	0.838
CDR score	1.922 (1.256, 2.941)	0.003	0.913 (0.664, 1.254)	0.573	1.955 (1.427, 2.679)	<0.001

Results are presented as HR and 95%CI.

* The Frailty Index (continuous variable) is included in the models as percentage in order to facilitate the reading of the results.

FI: Frailty Index; **CDR score:** Clinical Dementia Rating score; **n/N:** number of events/total study sample