TITLE
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JOURNAL
Journal of the American Geriatrics Society

DATE DEPOSITED
1 May 2018

This version available at
https://research.stmarys.ac.uk/id/eprint/2279/

Frailty Index and cognitive decline in Alzheimer's disease: data from the ICTUS study

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ABSTRACT

OBJECTIVES: Little is known about the role of frailty on the risk of greater cognitive decline in Alzheimer's disease (AD). We aimed to examine whether the Frailty Index (FI) was associated with short-term cognitive decline (assessed by the modifications of the Mini Mental State Examination-MMSE and Alzheimer's Disease Assessment Scale–Cognitive subscale-ADAS-Cog scores between 1-year of follow-up and baseline assessment) in AD patients. **DESIGN/SETTING:** Prospective cohort study among 973 subjects from the Impact of Cholinergic Treatment Use (ICTUS) study. **METHODS:** Changes in the MMSE and ADAS-Cog scores between 1-year of follow-up and baseline assessment were considered. The severity of dementia was assessed by the Clinical Dementia Rating score (CDR score). The FI score was calculated as the ratio of actual to potential deficits, i.e. deficits present in that person divided by 30. Linear regression analyses were performed, and also stratified by the severity of dementia. **RESULTS:** A 1 unit (0.033 points) increase in the FI corresponded to significant and clinically relevant cognitive decline, after adjustments for age, sex, and years of education, ranging between 0.63 and 4.63 points, P=0.010 in the MMSE score, and 2.87 and 11.1 points, P=0.001 in the ADAS-Cog score after 1 year of follow-up. The difference in the MMSE and ADAS-Cog variations between non-frail and frail individuals was 0.67 and 1.6 points, respectively. Although statically significant, the clinical relevance of this finding remains to be further investigated. **CONCLUSION:** Our findings suggest that the FI may represent a promising instrument for the assessment of the AD patients' vulnerability. Its implementation in the clinical practice may indeed support clinical decisions by identifying individuals at high risk of negative outcomes, specifically, short-term cognitive decline.

INTRODUCTION

Population aging is leading to a considerable increase in age-related pathological conditions, such as dependence and disability [1]. In this context, frailty has been attracting increasing scientific interest [2, 3]. Frailty is multiply determined, and characterized by decreased reserves and diminished resistance to stressors, due to the cumulative declines of multiple physiological systems [4]. For such characteristics, the concept of frailty offers a promising opportunity to move beyond the obsolete chronological criterion of age in the clinical decision process.

Among the most commonly used operational definitions of frailty, the model proposed by Rockwood and colleagues (the so-called "frailty index", FI) [5] is of particular interest. The FI is founded on the theoretical concept that frailty results from the accumulation of deficits. Its operationalization takes into account clinical signs, symptoms, diseases, disabilities, psychosocial risk factors, and geriatric syndromes, resulting in a score which is strongly associated with negative health outcomes (e.g., hospitalization, institutionalization, and death) in community-dwelling older persons [4]. In other words, the FI can be considered as an instrument to objectively measure individual age, based on how deficits accumulate, regardless of whether the deficits are considered as symptoms, signs, comorbidities or disabilities [6].

Accumulating evidence supports the existence of a close relationship between frailty and cognitive impairment in non-demented and demented subjects [7-15]. Nevertheless, less is known about whether frailty (as an accumulation of deficits) differentiates the risk of greater cognitive decline in a cohort of Alzheimer's disease (AD) subjects. Since the FI objectively reflects the biological age of the individual [16], it may significantly help in the clinical assessment of such extremely vulnerable and heterogeneous population. In fact, it may serve

as a parameter for improving the identification of older patients exposed to a particularly high risk of negative events.

The trajectory of cognitive decline in patients with AD is not linear, and inter- and intra-individual differences exist in the speed of cognitive loss in this population [17, 18]. Having an instrument that may support the clinician at identifying those who may quickly present a steeper decline of their cognitive functions is a difficult but important task.

In the present paper, we hypothesized that the FI may help at better identifying those AD patients who are at risk of cognitive decline, independently of chronological age and dementia severity. Therefore, our objective was to examine whether the FI, as a marker of biological aging, was associated with short-term cognitive decline (as assessed by the modifications of the MMSE and ADAS-Cog scores between 1-year of follow-up and baseline assessment) in a large sample of AD patients.

METHODS

Participants and study design

Data are from the Impact of Cholinergic Treatment USe (ICTUS) study [19]. Briefly, this 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.

Inclusion criteria were: 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 [20]; 2) MMSE score ranging from 10 to 26 [21]; 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.

A total of 1,375 patients were recruited in the ICTUS study. After the baseline assessment (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, comprehensive clinical and neuropsychological assessments were performed. Current analyses were performed in 973 subjects. Patients who were excluded (n=402) were not different in relation to age 76.6 (±7.7) years, and years of education 7.93 (±4.46) years compared to those included in the study 76.2 (±7.7) years, P=0.88 and 7.97 (±4.69) years, P=0.31, respectively. They also had a higher mean FI (FI=0.23 points) compared to those included (FI=0.20 points), P=0.003; higher CDR score 1.00 (±0.58)

vs 0.90 (±0.47), P=0.001; lower MMSE score 20.0 (±4.2) vs 20.6 (±3.8) points, P=0.03 and higher ADAS-Cog score 23.1 (±10.8) vs 20.2 (±9.0) points, P<0.001.

Data on modifications of the MMSE score were available for n=1,005 patients and of the ADAS-Cog score for n=979 patients. In order to consistently explore our study hypotheses in a well-defined sample, the present analyses were conducted only considering those patients with complete data on both the MMSE and ADAS-Cog scores at baseline and 1-year follow-up visit. This approach resulted to the additional exclusion of 32 patients with ADAS-Cog data, but missing for the MMSE ones; and 6 patients who had MMSE data but missing for the ADAS-Cog variation.

Assessment of cognitive function

Changes in the MMSE and ADAS-Cog scores between 1-year of follow-up and baseline assessment were considered as the outcome variables of interest. The decision to censor follow-up after the first year was taken for multiple reasons. The objective of the study was to explore the clinical relevance of the FI. In AD patients (characterized by high vulnerability and instability) prevention of negative short-term events becomes particularly relevant, and has an important impact on clinical decision-making. Moreover, the restriction to only the first year of follow-up may reduce the number of potential intermediary events altering the association between the FI and the studied outcomes. In fact, the longer follow-up may be associated with a higher number of intermediary events potentially biasing the interpretation of the results. Such a conservative approach is also related to the heterogeneity of AD patients (in terms of phenotypic manifestations, trajectories of cognitive decline, and clinical stability), which exposes the individual to a wide spectrum of often unforeseeable events. This approach has been previously used in the ICTUS cohort for obtaining a more reliable interpretation of findings [22].

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The MMSE score is a commonly used psychometric screening assessment tool of cognitive functioning and consists of 30 points grouped into seven categories, with a lower score indicating greater cognitive impairment [23]. The ADAS-Cog is widely adopted for assessing cognitive function in patients with AD in clinical practice and research [24, 25]. This scale includes 11 components, each of which assesses a relevant aspect of cognitive dysfunction in AD. After summing up all 11 components, a scale from zero to 70 is constructed, with a higher score indicating greater cognitive impairment.

In order to account for the influence of baseline severity, analyses were stratified according to the CDR score. The CDR scale is an instrument which assesses the severity of dementia along 5 levels of impairment (rated as 0, 0.5, 1, 2 or 3) in each of 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. CDR global ratings, range from 0 (no dementia) to 3 (severe dementia) [26]. For the present analyses, the sample population was divided into two CDR groups: CDR=0.5 (very mild AD) and CDR≥1 (mild to severe AD) [27]. None of the patients in the ICTUS study presented a CDR score equal to 0 due to the applied eligibility criteria.

Independent variable of interest

The FI was generated from the baseline assessment data. Each deficit included in the FI (**Appendix**) was coded so that a value of 0 indicates the absence of the deficit and a value of 1 its presence. Overall, 30 variables were employed which typically is sufficiently robust for accurate computation of the FI [28, 29]. Each individual's FI score was calculated as the ratio of actual to potential deficits, i.e. deficits present in that person divided by 30. Thus, the FI ranged between 0 (no deficit is present) and 1 (all the deficits are present), with an increment of 0.033 points corresponding to the presence of one additional deficit among the 30 considered.

Other variables

Socio-demographic (age, gender, education), current use of cholinesterase inhibitors, cognitive and functional measurements recorded at the baseline assessment are here used for describing the study sample.

Statistical analysis

Means and standard deviations (SD) or percentages were used to describe baseline characteristics of the study sample. Linear regression analyses were used to estimate the beta coefficients and 95% confidence intervals (95%CI) relating the FI and change in MMSE and ADAS-Cog scores over 1-year of follow-up. Analyses were also stratified by the severity of dementia (CDR=0.5 vs. CDR≥1). Unadjusted and adjusted univariate analyses of covariance were then performed for estimating means and standard errors (SE) of the MMSE and ADAS-Cog scores across a dichotomous FI variable (FI<0.25 vs. FI ≥0.25) [30]. Results from the unadjusted and age-, gender- and education-adjusted models are provided. Statistical significance was set at a p value<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*=973) at baseline (**Table 1**) indicate an older sample (mean age 76.2 (SD 7.7) years, of mostly women (64.3%). The mean FI was 0.20 (SD 0.12) points, ranging between 0 and 0.63. Patients showed mild-moderate cognitive impairment at baseline with mean ADAS-Cog and MMSE scores of 20.2 (SD 9.0) and 20.6 (SD 3.8), respectively. Almost 90% of participants had a CDR score equal to 0.5 or 1, and the remaining had more severe stages of AD.

A higher FI was associated with greater cognitive decline as assessed by both the MMSE and ADAS-Cog variations over the follow-up (**Table 2**). Associations were not attenuated after adjustments for age, gender and years of education for the MMSE [beta: -2.63 (95%CI: -4.63, -0.63), P=0.010], and ADAS-Cog [beta: 6.96 (95%CI: 2.87, 11.1), P=0.001] variations. Alternatively, a 0.033 points increase in the FI corresponds to 2.63 points and 6.96 points of decline in the MMSE and ADAS-Cog scores, respectively after 1 year of follow-up. Interactions of the FI and cognitive function with age, gender, years of education and CDR score were not statistically significant (all p values for interaction terms >0.05). However, to describe the cognitive decline, trajectories in specific subgroups according to the severity of dementia are presented (**Table 2**).

Subjects with mild to severe AD (CDR≥1) showed a greater cognitive decline for increasing FI, which was not significant for both the MMSE variation [beta: -2.33 (95%CI: -4.94, 0.28), P=0.080], and the ADAS-Cog variation [beta: 5.34 (95%CI: -0.42, 11.1), P=0.069].

The unadjusted and adjusted estimated mean variations of MMSE and ADAS-Cog scores (between the 1-year follow-up visit and the baseline assessments) for non-frail and frail subjects are reported in **Table 3**. For both outcomes, being frail (FI>0.25 points; *n*=323, 33.2%) was associated with significant cognitive declines (P<0.05 for all).

Finally, we checked whether our findings could have been different if additional including those participants with valid data for only the ADAS-Cog (n=32) or only the MMSE (n=6) variations. No substantial differences from what here reported were observed (results available upon request).

DISCUSSION

In the present study, we demonstrated that in AD patients the FI is significantly associated with greater cognitive decline, as observed on the MMSE and ADAS-Cog scores. To our knowledge, this is the first independent study to apply the FI model to an AD population. Our findings suggest that the FI may represent a robust instrument for identifying older individuals at increased risk of greater cognitive decline.

Our results showed that the 99% upper limit of the generated FI score (0.63) in our AD sample was between the range of 0.6-0.7 points as previously observed in community and institutionalized older populations [31]. In this study it was observed that even if the FI is adapted to a different population, it still maintains the consistency of remaining below the threshold of 0.7 points, which determines the compatibility with life. Therefore, reports from community-dwelling populations on the FI are also confirmed here in an AD population. It might also be suggested that this finding may provide a kind of biological "signature" for the FI.

In our study, a 0.033 points increase in the FI was associated with a clinically relevant worsening of cognitive performance. In fact, the addition of only one deficit in the FI was associated with a decrease in the MMSE score of 2.6 points over the first year of follow-up. This result may be considered clinically relevant. In this context it has been shown that a change of MMSE score between 2 and 4 points could be considered as clinically reliable [32]. Furthermore, a threshold of 2 MMSE points in 1 year has been used to clinically identify a decline in AD patients, allowing differentiating AD patients as slow and rapid progressors [33]. Accordingly, a recent meta-analysis of randomized controlled trials has estimated that the mean annual gain of ADAS-Cog score was 5.5 points in mild to moderate AD patients [34]. In our study, we found that subjects with a higher FI showed a mean annual increase of

ADAS-Cog score of 6.96 points. Such datum may provide an idea of the clinical relevance of the FI in determining the cognitive decline of AD patients.

Furthermore, when the Frailty Index was considered as categorical variable (independently of the severity of the condition) we did not observe important differences in cognitive decline over time. Indeed, a difference of 0.67 points in the MMSE (adjusted model) between the non-frail and frail individuals may be small; however, its clinical significance may be arguable and needs to be further clarified and explored in future ad hoc studies. Therefore, based on these results it would be important to consider not only the presence or absence of frailty but also the severity and the number of deficits formulating the Frailty Index. This gives valuable information for future cognitive decline of mild to moderate AD patients, and gives the opportunity to the clinician to predict a clinically important change of cognitive function.

Also, in order to take into account the weight that the baseline severity of the main condition (i.e., AD) may play in the interpretation of the findings, analyses were further stratified according to the CDR score. Although, the limited number of severely demented patients (10.8%) does not allow us to draw firm conclusions and results were not significant, however, there was a trend showing that higher FI was associated with greater worsening in cognitive performance in patients with mild to severe AD (CDR≥1). Moreover, dementia severity strongly influences the main clinical manifestations of AD and stratifying analyses by the CDR score has been previously largely used to better account the heterogeneity of this complex population [35].

The need for adapting clinical care to the specific needs of older patients requires instruments capable of perceiving the inner biological age that extend from model organisms to human populations [36]. In this context, the FI may open interesting and promising scenarios in the field of neurodegenerative diseases, conditions that are particularly burdening for the persons,

their families, and public healthcare. The AD patients form quite a heterogeneous population and patients may follow different trajectories of the progression of the disease. The FI responds to the need of adapting standard instruments for such a complex typology of patients. In fact, different from other frailty instruments, it can be applied to every individual, independently of age, comorbidities, and functional status. Moreover, the increasing use of electronic medical records in the healthcare settings may facilitate the adoption of such objective parameters, with the purpose of supporting clinical decisions, even over time. For example, we can imagine that the routine data collection conducted by the healthcare professionals may lead to the automatic generation of the FI, thus supporting clinicians in the development of the personalized intervention plans. In fact, the identification of AD individuals with a high FI (that are at risk of greater cognitive decline over the short-term) may solicit the design of immediate actions and close follow-up. The ability to improve the definition of the patient's risk profile through the use of the FI may indeed facilitate the optimization of interventions and allocation of resources in a complex population such as the one affected by AD.

Although the theoretical foundations of frailty are well established, its implementation is still controversial, especially in the clinical practice. Compared to the well-known "frailty phenotype" proposed by Fried and colleagues (based on the evaluation of five defining criteria: weight loss, sedentary behaviour, weakness, slow gait speed, and exhaustion) [37], the FI is characterized by a greater discriminatory capacity of the risk of negative health outcomes [4, 38]. Moreover, although the frailty phenotype is made up of relatively simple tasks for older individuals, it may still be quite challenging for individuals with dementia, or at least poorly reliable. For example, the cognitive impairment of the patient may limit his/her ability to adequately perform the physical function tests or provide consistent answers about perceived symptoms or behaviors. It is also noteworthy that the FI may include disabilities in

its computation [6]. This aspect is particularly interesting in a condition such as AD where disabilities are highly prevalent and concur at the determination of the individual's risk profile.

Our study has limitations worth to be mentioned. Due to the nature of the study causal associations cannot be inferred. The representativeness of our study sample makes the significant association reported between the FI and cognitive decline applicable to community-dwelling patients with AD. The translation of our results in different settings (e.g., hospital, nursing homes) and clinical conditions (other than AD) should be confirmed by ad hoc analyses. Moreover, our results might have been underestimated as persons who dropped-out of the study appeared to be frailer compared to those included.

In conclusion, our findings suggest that the FI may represent a promising instrument for the assessment of the AD patients' vulnerability. Its implementation in the clinical practice may indeed support the clinical decisions by identifying individuals at high risk of negative outcomes (in particular, short-term cognitive decline) in such heterogeneous and complex population.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

None declared.

Author's contributions

Study conception and design: SA and BV. *Acquisition, analysis, or interpretation of data*: EK, MC, MC. *Drafting of the manuscript*: EK. *Critical revision of the manuscript for important intellectual content*: EK, MC, SA, NDC, MES, BV, MC. *Final approval:* EK, MC, SA, NDC, MES, BV, MC. *Study supervision*: MC, SA and BV.

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Table 1. Baseline characteristics of the study sample.

	Means ± SD, or percentage (*n*=973)
Age (years)	76.2±7.7
Gender (women)	64.3
Body mass index (kg/m^2)	25.2±4.0
Education time (years)	8.0±4.7
Current ChEI use	49.2
ADAS-Cog (points)	20.2±9.0
MMSE (points)	20.6±3.8
CDR score	
- 0.5	43.3
- 1	45.9
- ≥2	10.8
ADL (/6)	5.5±0.8
IADL (/8)	4.9±2.2
Frailty Index (0-1 scale)	0.20±0.12

Values are presented as means ± standard deviations (SD) or percentage. **AD:** Alzheimer's disease; **ChEIs:** Cholinesterase Inhibitors; **ADAS-Cog:** Alzheimer's Disease Assessment Scale – Cognitive subscale; **MMSE:** Mini Mental State Examination; **CDR:** Clinical Dementia Rating; **ADL:** Activities of Daily Living; **IADL:** Instrumental Activities of Daily Living.

Table 2. Results from linear regression analysis between the Frailty Index and cognitive decline.

	Δ MMSE Between 1 year follow-up & baseline assessment		Δ ADAS-Cog Between 1 year follow-up & baseline assessment	
	B coefficient (95%CI)	P	B coefficient (95%CI)	P
Frailty Index (continuous)				
Unadjusted	-2.31 (-4.24, -0.39)	0.019	6.03 (2.09, 9.96)	0.003
Adjusted for age, gender	-2.64 (-4.61, -0.66)	0.009	7.19 (3.16, 11.2)	<0.001
Adjusted for age, gender, education	-2.63 (-4.63, -0.63)	0.010	6.96 (2.87, 11.1)	0.001
Stratified by CDR score (adjusted for age, gender, education)				
- 0.5 (*n*=421)	-1.16 (-4.65, 2.33)	0.513	4.22 (-1.99, 10.4)	0.183
- ≥ 1 (*n*=551)	-2.33 (-4.94, 0.28)	0.080	5.34 (-0.42, 11.1)	0.069

Δ MMSE: Difference in Mini Mental State Examination test between 1 year of follow-up and baseline assessment; **Δ ADAS-Cog:** Difference in Alzheimer's Disease Assessment Scale – Cognitive subscale between 1 year of follow-up and baseline assessment.

Table 3. Longitudinal modifications of ADAS-Cog and MMSE scores according to the frailty status.

	Baseline MMSE	Δ MMSE Between 1 year follow-up & baseline assessment[1]		Baseline ADAS-Cog	Δ ADAS-Cog Between 1 year follow-up & baseline assessment[1]	
	Mean±SEM (range)	Unadjusted Mean±SEM	Adjusted[2] Mean±SEM	Mean±SEM (range)	Unadjusted Mean±SEM	Adjusted[2] Mean±SEM
Non-frail: ≤ 0.25 points (*n*=650)	21.13±0.15 (10-26)	-1.24±0.14	-1.24±0.15	18.74±0.34 (5-55)	3.07±0.29	3.06±0.30
Frail: > 0.25 points (*n*=323)	19.58±0.21 (11-26)	-1.89±0.20	-1.91±0.21	23.20±0.48 (2-62)	4.59±0.42	4.66±0.42

Δ MMSE: Difference in Mini Mental State Examination test between 1 year of follow-up and baseline assessment; **Δ ADAS-Cog:** Difference in Alzheimer's Disease Assessment Scale – Cognitive subscale between 1 year of follow-up and baseline assessment; **SEM:** standard error of means;

[1]Values are presented as means ± SEM. All statistical differences were statistically significant (all p values<0.05) between frail and non-frail participants.

[2]Adjusted for age, gender and years of education.

List of the 30 variables composing the Frailty Index (FI)

1. Diabetes

2. Hypercholesterolemia

3. Hypertension

4. Ischemic heart disease

5. Depression

6. Stroke

7. Falls

8. Seizures

9. One leg balance

10. Parkinsonism

11. Focal signs

12. Help bathing

13. Help dressing

14. Help using toilet

15. Help getting in/out of chair

16. Continence

17. Help eating

18. Help taking medications

19. Delusions

20. Hallucinations

21. Agitation/aggression

22. Dysphoria

23. Anxiety

24. Elation/euphoria

25. Apathy

26. Disinhibition

27. Irritability/lability

28. Aberrant motor behaviour

29. Sleep

30. Appetite and eating disorders