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A frailty index based on laboratory deficits in community-dwelling men predicted their risk of adverse health outcomes

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Abstract

Background: abnormal laboratory test results accumulate with age and can be common in people with few clinically detectable health deficits. A frailty index (FI) based entirely on common physiological and laboratory tests (FI-Lab) might offer pragmatic and scientific advantages compared with a clinical FI (FI-Clin).
Objectives: to compare the FI-Lab with the FI-Clin and to assess their individual and combined relationships with mortality and other adverse health outcomes.
Design and subjects: secondary analysis of the eight-centre, longitudinal European Male Ageing Study (EMAS) of community-dwelling men aged 40–79 at baseline. Follow-up assessment occurred 4.4 ± 0.3 (mean ± SD) years later.
Methods: we constructed a 23-item FI using common laboratory tests, blood pressure and pulse (FI-Lab), compared it with a previously validated 39-item FI using self-report and performance-based measures (FI-Clin) and finally combined both FIs to create a 62-item FI-Combined. Outcomes were all-cause mortality, institutionalisation, doctor visits, medication use, self-reported health, falls and fractures.
Results: the mean FI-Lab score was 0.28 ± 0.11, the FI-Clin was 0.13 ± 0.11 and FI-Combined was 0.19 ± 0.09. Age-adjusted models demonstrated that each FI was associated with mortality [HR (CI) FI-Lab: 1.04 (1.03–1.06); FI-Clin: 1.05 (1.04–1.06); FI-Combined: 1.07 (1.06–1.09)], institutionalisation, doctor visits, medication use, self-reported health and falls. Combined in a model with FI-Clin, the FI-Lab remained independently associated with mortality, institutionalisation, doctor visits, medication use and self-reported health.
Conclusions: the FI-Lab detected an increased risk of adverse health outcomes alone and in combination with a clinical FI; further evaluation of the feasibility of the FI-Lab as a frailty screening tool within hospital care settings is needed.

Keywords: *frailty, frail older people, pre-clinical frailty, ageing, mortality*

Introduction

Ageing reflects an accumulation of continuous health deficits that culminate in an increased risk of death. Although affected by lifestyle factors across the life course, ageing occurs independently of external, environmental factors. The complexity of genetics [1] and differences in developmental and environmental factors affect the rate of ageing at a microscopic level [2]. Clinical manifestations of ageing are understood to arise in relation to proximal damage—beginning at the organ, tissue, cellular, subcellular and molecular levels [3]. Even so, how damage at those levels results in clinically detectable, age-related deficits is unclear [4].

Considered individually, cellular and tissue biomarkers show little relationship with ageing and frailty [5]. Recent reports suggest that, taken together, subclinical deficits are related to adverse outcomes of ageing and precede clinically evident health deficits [4, 6, 7]. Those studies reported that combining subclinical deficits (laboratory test abnormalities, ageing biomarkers) in a frailty index (FI), even including

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deficits not individually related to death, were significantly associated with mortality risks, independently of a clinical FI. In short, the clinically detectable health deficits that have, until now, laid the basis for understanding frailty (all frailty measures count deficits and show broadly similar characteristics [8]) appear to be preceded by subclinical abnormalities, some of which can be captured by laboratory measurements commonly encountered in clinical practice.

The first reports to combine laboratory test abnormalities in an FI used Canadian data on older adults collected in 1991–92 and over-represented people with cognitive impairment [6, 7] and evaluated mortality and institutionalisation as outcomes. The case for laboratory and test measures preceding clinically evident ones would be strengthened by more contemporary data examining this relationship in less catastrophic adverse health outcomes. In consequence, we explored the relationship between subclinical deficit accumulation and clinically visible deficits, and evaluated their individual and joint impact on a range of adverse health outcomes. In this secondary analysis of community-dwelling men in the European Male Aging Study (EMAS), our objectives were (i) to develop an FI consisting of standard laboratory tests as well as blood pressure and pulse (FI-Lab); (ii) to examine the predictive ability of the FI-Lab in relation to mortality and more proximal adverse health outcomes including healthcare utilisation, medication use, fractures, falls and self-reported health and (iii) to compare the predictive ability of the FI-Lab and an FI based on self-reported, performance based and clinically detectable deficits (FI-Clin).

Table 1. Study sample characteristics (n = 2,933)

	Mean (SD)
Age at baseline (years)	60.2 (10.9)
Height (cm)	173.7 (7.3)
Weight (kg)	83.5 (13.8)
Body mass index (kg/m^2)	27.7 (4.06)
	Per cent (%)
Smoking	
Never smoked	29.6
Former smoker	50.2
Current smoker	20.2
Alcohol consumption	
Never	35.2
≤2 days/week	20.8
≥3 days/week	44.0
Education	
Primary	2.6
Secondary	43.7
Higher	53.7
Partner status	
Spouse or partner	91.5
No partner	8.5
Study centre	
Florence, Italy	13.3
Leuven, Belgium	13.8
Lodz, Poland	12.0
Malmo, Sweden	12.7
Manchester, UK	11.6
Santiago, Spain	11.7
Szeged, Hungary	13.0
Tartu, Estonia	11.8

Methods

Participants, setting and sample

EMAS, a multi-centre, prospective cohort study, examined a probability sample of 3,369 community-dwelling men (60 ± 11, range 40–79 at baseline). Stratified random sampling was used to recruit equal numbers of men across age ranges (40–49, 50–59, 60–69 and 70–79 years) from population registers in eight countries (Table 1); there were no specific exclusion criteria. EMAS chiefly examined risks and outcomes associated with age-related decline in male endocrine function [9]. All participants completed a postal questionnaire about general health, education and physical activity between 2003 and 2005. They each had a baseline clinical examination with an interviewer-assisted health questionnaire, physical, visual and cognitive function tests, anthropometry and a fasting blood sample. Questionnaire and clinical data were repeated between 2007 and 2009. Ethical approval for EMAS was obtained following each centre's institutional requirements; all participants provided written informed consent whenever primary data were collected.

Frailty measures

We employed three FIs, including a previously validated FI-Clin, constructed from 39 self-reported and performance-based measures collected using questionnaire and clinical examination data at baseline [10] (Supplementary data, Table 1, available in Age and Ageing online). Next, we created the 23-item FI-Lab from routine blood tests and measured blood pressure and pulse rate. Normal reference intervals were used to code each variable [11]; any value lying outside of the reference range was scored '1', as a deficit (Supplementary data, Table 2, available in *Age and Ageing* online) [6]. Finally, we combined the two FIs to create a 62-item FI (FI-Combined). In each case, the FI was calculated as the number of deficits in an individual divided by the total number of deficits measured.

Frailty scores were calculated only for individuals with 80% of the data on each FI. As no standard frailty cut points have been validated for the FI-Lab, although analysed as a continuous variable (below), for presentation purposes, frailty scores were categorised incrementally as: <0.1, 0.1–0.2 0.2–0.3, 0.3–0.4 and >0.4.

Outcomes

The primary outcome, all-cause mortality, was verified from death certificates, death registers, medical/hospital records and, if needed, contact with family members. Secondary outcomes were institutionalisation, healthcare use, medication use, fractures, falls and a self-rated summary health question. Healthcare use was considered high for 4+ self-reported doctor visits in the past 12 months and low if respondents

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answered 'almost never' or 'only very rarely' [12]. Individuals in the highest 10% (5 or more) were considered taking a high number of medications, which is common in frailty [13]. New fractures and falls since baseline (also linked to frailty) [14] were dichotomised as any versus none. Poor self-reported health was indicated by responses 'fair' or 'poor' when asked about general health. As self-reported health was an item within the FI-Clin and FI-Combined, it was excluded from the calculation of the FI when analysed as an outcome.

Statistical analysis

We used IBM SPSS Statistics, Version 22; for graphs R, Version 3.1.3 and SigmaPlot 13.×. An alpha level <0.05 indicated statistical significance. For each FI, density distributions were plotted and summary statistics calculated, including the 99% limit to the FI [15]. The mean of each FI score at each age was plotted to examine the age association of all FIs; data were fitted with a logarithmic curve. The slope of a linear regression through the natural logarithm of the FI score at each age was evaluated to compare the rate of increase in deficit accumulation with age by FI.

Having verified proportionality, age-adjusted proportional hazard models were used to examine the impact of FI scores on all-cause mortality. Increase in risk by a 0.01 increase in the FI score was examined by multiplying each FI score by 100 and then converting scores to integers (0–100). Kaplan–Meier survival curves were plotted by FI group, and statistical significance was evaluated with a log-rank test. To compare each FI's discriminant ability, we calculated the area under the receiver operating characteristic (ROC) curves for mortality. Age-adjusted logistic regression examined the association between each baseline FI and all secondary outcomes. Individuals with the adverse outcome at baseline were excluded from outcome-specific regression analyses, save for health utilisation, falls and fractures, which were not collected at baseline.

Results

Of the initial 3,369 participants, 334 were lost to follow-up and did not participate in the study at Wave 2. Those lost to follow-up (58.0 ± 11.6 years; mean FI-Lab = 0.27 ± 0.11; mean FI-Clin = 0.13 ± 0.10; mean FI-Combined = 0.18 ± 0.09) were younger ($P < 0.05$) than the study sample (60.2 ± 10.9 years; mean FI-Lab = 0.28 ± 0.11; mean FI-Clin = 0.13 ± 0.11; mean FI-Combined = 0.18 ± 0.09), with no difference in any FI score at baseline. Of the remaining 3,035 participants, 102 did not have sufficient frailty data (≥80% of variables) in one or more FI, leaving 2,933. Participants with inadequate frailty data (62.3 ± 11.2 years) were older ($P = 0.05$) and showed higher mortality (12.7 versus 6.7%; $P < 0.05$) but similar rates of institutionalisation (3.3 versus 3.7%; $P = 0.83$). With each FI, as the baseline frailty scores increased, so did mean age. Frailty scores increased by 4.1% (FI-Clin), 1.0% (FI-Lab) and 2.3% (FI-Combined; Supplementary data, Figure 1A, available in *Age and Ageing* online) each year on a logarithmic scale.

The FI-Clin and the FI-Lab were significantly but relatively weakly correlated (Pearson $r = 0.33$; $P < 0.001$). The distribution of the FI-Clin was skewed with a long right tail, whereas the FI-Lab had a less skewed distribution; the distribution of the FI-Combined was intermediate between the former two (Figure 1A; Supplementary data, Figure 1B, available in *Age and*

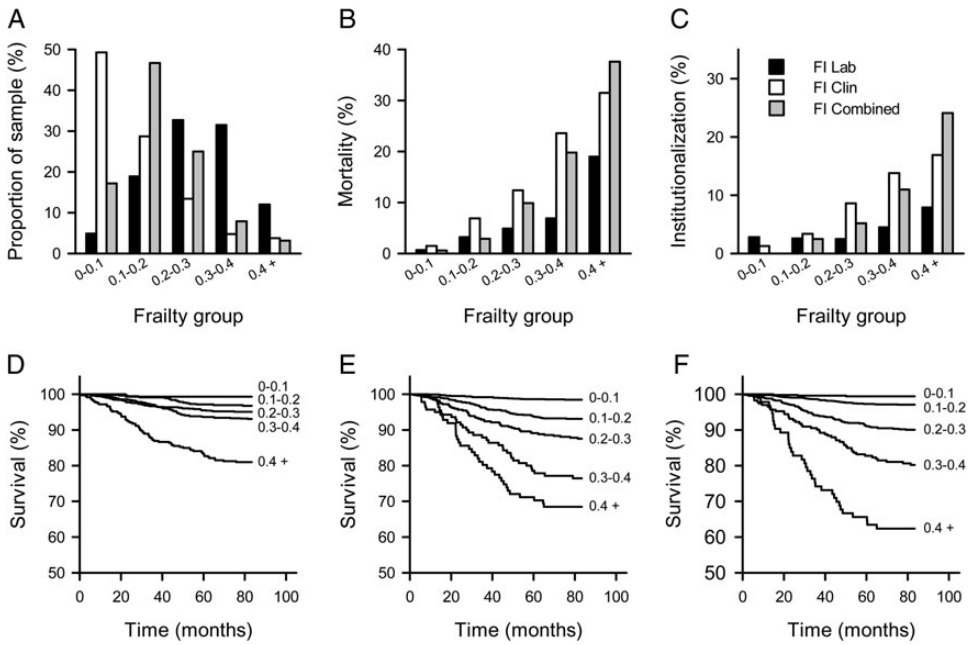

Figure 1. Proportion of sample size in each frailty group (A). Prevalence of mortality and institutionalisation by frailty group (B and C). Kaplan–Meier survival curves for FI-Lab (D), FI-Clin (E) and FI-Combined (F) by frailty groups. Differences between frailty groups were statistically significant for all three indices using the log-rank test ($P < 0.001$).

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Ageing online). The mean FI-Clin score was 0.13 ± 0.11 (range 0.00–0.68), lower than the FI-Lab (0.28 ± 0.11; range 0.00–0.74) and the FI-Combined (0.19 ± 0.09; range 0.00–0.69). The 99th percentile scores were 0.50, 0.56 and 0.47, respectively.

Mortality and institutionalisation rates increased as each FI score increased ($P < 0.001$; Figure 1B and C). Age-adjusted Cox regression models demonstrated that each FI was significantly associated with mortality (Table 2). For all outcomes, the hazard ratio for each 0.01 frailty score increase was lower for the FI-Lab (Table 2, Model 1) than for the FI-Clin (Table 2, Model 2); both remained significant when included in the same model (Table 2, Model 4). The FI-Combined had the highest hazard ratios in Cox regression models (Table 2, Model 3). Likewise, the Kaplan–Meier curves revealed a significant separation in frailty groupings for all FIs (Figure 1D–F) with the FI-Combined showing the clearest separation. Finally, the ROC curves showed an increase in discriminative ability for mortality when the FI-Lab and FI-Clin were combined; the areas under the ROC curve (AUC) were 0.70 (0.66–0.74), 0.79 (0.76–0.82) and 0.81 (0.78–0.84) for the FI-Lab, FI-Clin and FI-Combined, respectively ($P < 0.01$). AUC curves for secondary outcomes ranged from 0.50 to 0.65 for the FI-Lab, 0.56 to 0.81 for FI-Clin and 0.54 to 0.80 for FI-Combined (see Supplementary data, Table 3, available in *Age and Ageing* online).

All three FIs significantly predicted institutionalisation, frequency of doctor visits, higher medication use, falls and poor self-reported health (Table 2). Only the FI-Clin and the FI-Combined significantly predicted fractures (see Table 2). In a combined model (Table 2; Model 4), the FI-Lab remained significantly associated with frequency of doctor visits, self-reported health and number of medications independent of the FI-Clin.

Discussion

We created a 23-item FI- Lab from common laboratory tests, blood pressure and pulse measures, and demonstrated that it had similar properties to the previously validated FI-Clin, which consisted of clinically detectable deficits, self-reported items, and balance and mobility measures. Mean FI-Lab scores were higher than mean FI-Clin scores, with a wider distribution across the population sample. Lower FI-Clin scores were expected, given the relatively young age of the sample [16]. The higher FI-Lab scores are consistent with this, reflecting an intermediate step linking cellular ageing to clinically detectable deficits, as also shown by the less skewed distribution. So too is the significant, if slightly lower, ability of the FI-Lab, compared with that of the FI-Clin, to predict a range of other health outcomes, including, in age-adjusted multivariable models of risk of death, institutionalisation, greater medication use, more physician visits and lower self-rated health.

Our data must be interpreted with caution. EMAS studied only men in some European countries. Response bias is likely, given the 41% overall participation rate [9]. Building on usual care, laboratory testing was done locally, not centrally, although arguably this improves feasibility. There continues

Table 2. Age-adjusted predictive models for mortality (Cox regression) and secondary outcomes (logistic regression; HR and OR estimates are for each 0.01 FI increase)

	Mortality ($n = 2,933$)	Institution-alisation ($n = 2,751$)	Frequency of doctor visits ($n = 2,550$)	High number of medications ($n = 2,634$)	Poor self-reported health ($n = 2,489$)	Fractures ($n = 2,549$)	Falls ($n = 2,565$)
Prevalence of deficit at follow-up (%)	6.7	3.7	47.4	13.4	2.5	5.3	27.2
Regression Model 1							
FI-Lab	1.04 (1.03–1.06)*	1.02 (1.00–1.04)*	1.03 1.02–1.04)*	1.04 (1.02–1.05)*	1.03 (1.02–1.05)*	1.00 (0.99–1.02)	1.01 (1.00–1.02)*
Regression Model 2							
FI-Clin	1.05 (1.04–1.06)*	1.04 (1.03–1.06)*	1.09 (1.08–1.10)*	1.04 (1.03–1.05)*	1.08 (1.06–1.10)*	1.03 (1.02–1.05)*	1.05 (1.04–1.06)*
Regression Model 3							
FI-Combined	1.07 (1.06–1.09)*	1.06 (1.04–1.08)*	1.10 (1.09–1.12)*	1.06 (1.04–1.07)*	1.10 (1.07–1.13)*	1.04 (1.02–1.06)*	1.06 (1.04–1.07)*
Regression Model 4							
FI-Lab	1.03 (1.02–1.04)*	1.01 (0.99–1.03)	1.02 (1.01–1.03)*	1.03 (1.02–1.04)*	1.02 (1.01–1.04)*	1.00 (0.98–1.01)	1.00 (0.99–1.01)
FI-Clin	1.04 (1.03–1.05)*	1.04 (1.03–1.06)*	1.09 (1.07–1.10)*	1.03 (1.02–1.04)*	1.08 (1.06–1.10)*	1.03 (1.02–1.05)*	1.05 (1.04–1.06)*

Age was significant at $P < 0.05$ for all four models for mortality, institutionalisation, frequency of doctor visits and high number of medications.
*$P < 0.05$.

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to be discord about general reference ranges for laboratory values [17] from which our standard ranges [12] are not exempt. Loss to follow-up was 9.9%, biased towards slightly younger participants, whose mean frailty scores did not differ significantly for either the FI-Clin or FI-Lab. We assessed the FI-Lab as a measure of subclinical frailty by examining how this measure can predict adverse health outcomes. Future research should examine the accuracy of the FI-lab to capture the ability of an individual to respond and recover from stressors.

The prospective design and the multi-disciplinary range of data on various health domains including laboratory variables from nearly 3,000 subjects from a range of countries in the EMAS dataset have allowed the association between frailty and a variety of health domains to be explored. Earlier EMAS reports showed that the FI-Clin is associated with mortality [10] and impaired sexual functioning [18], but other outcomes have not been examined. Similarly most frailty papers are focusing on the ability of the frailty tools to predict mortality, and findings on other outcomes are limited [19]. The present study showed that the FI-Clin predicted institutionalisation, frequency of doctor visits, higher medication use, new falls since baseline and poor self-reported health. The FI-Clin and the FI-Combined also predicted fractures since baseline. Interestingly, the FI-Lab independently predicted mortality, frequency of doctor visits, number of medications and self-reported health. Results of the mortality prediction analysis suggest that pre-clinical deficits, as detected by the FI-Lab, independently contribute to pathological pathways leading to death. These results also indicate that a combined FI consisting of both clinical/macroscopic deficits and pre-clinical/microscopic deficits is a stronger predictor of death than the clinical/macroscopic FI on its own. The present findings are consistent with previous reports that the FI-Lab predicted mortality in a population including individuals with cognitive impairment [6, 7]. In EMAS, the FI-Lab added further accuracy (sensitivity and specificity) to predicting adverse health outcomes as it remained significant even when the clinical frailty score was included in the model.

Clinical deficits represent the expression of unrepaired and/or unremoved insults [20, 21], which reflects widespread, time-dependant damage at the subcellular, tissue and organ levels [22, 23]. This concept suggests that deficits at the molecular or cellular level will eventually scale up to visible macroscopic organ dysfunction [20]. Frailty can therefore be regarded as a dynamic process, originating at subcellular levels, affecting tissue, organ and eventually overall organism function [20, 23]. Recognising frailty has become synonymous with the clinical assessment of functional deficits in individuals at higher risk of adverse outcomes [8]. Being able to predict who are at risk prior to clinical manifestations has long been a goal; the FI-Lab, as a measure of pre-clinical frailty, might help shed some light on this.

Whereas many groups are revaluating individual biomarkers as precursors to poor health and eventual death [4], the FI-Lab allows some insight into the general health of an individual. This is consistent with a key premise of the FI, namely that the redundancy of the human organism means decrements are detected by examining many domains, rather than single ones, even for complex constructs such as disability, cognition and co-morbidities. Although specific test abnormalities can be helpful in examining particular areas of biological health, single biomarkers are unlikely to help us characterise overall fitness or frailty [4, 7]. The FI-Lab and FI-Clin are weakly correlated, indicating that although related they are distinct concepts.

Constructing an FI from laboratory data commonly collected in clinical settings may be easier than constructing FIs based on clinical assessment, but they yield information only about risk stratification, and they do not provide the level of detail needed to construct care plans. In this, whatever their performance in prediction or discrimination might be, they will have lesser utility than an FI based on a geriatric assessment. Even so, both viewing frailty as a long-term condition, [24, 25] and using it in the many clinical settings in which early identification of at-risk individuals is important, [26–29] make it likely that a quick means of extending our understanding of the degree of frailty to a subclinical level will be rewarding.

In conclusion, the results of the present and other related studies [30] suggest that combining laboratory test data with information taken from routinely collected clinical information about baseline cognition, function and mobility might more accurately assess frailty in routine care, while optimising feasibility. This interesting possibility is motivating further inquiry by our group.

Key points

- We constructed a frailty instrument from common laboratory tests, pulse and blood pressure measures (FI-Lab).
- The FI-Lab had properties similar to a previously validated FI consisting of clinically detectable deficits.
- The FI-Lab can identify individuals at risk of death and other adverse outcomes.
- The FI-Lab was able to identify those at increased risk of most adverse outcomes, independently of clinical frailty.
- Identifying pre-clinical frailty might aid in mitigating decline in health before it presents at a macroscopic, clinical level.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Conflicts of interest

None declared.

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