ORIGINAL RESEARCH

Operationalizing a frailty index using routine blood and urine tests

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Background: Uncomplicated frailty instruments are desirable for use in a busy clinical setting. The aim of this study was to operationalize a frailty index (FI) from routine blood and urine tests, and to evaluate the properties of this FI compared to other frailty instruments.

Materials and methods: We conducted a secondary analysis of a prospective cohort study on 306 patients aged ≥65 years hospitalized on geriatric wards. An FI comprising 22 routine blood parameters and one standard urine parameter (FI-Lab), a 50-item FI based on a comprehensive geriatric assessment (FI-CGA), a combined FI (FI-combined [items from the FI-Lab + others from the FI-CGA]), the Clinical Frailty Scale, rule-based frailty definition, and frailty phenotype were operationalized from data obtained during patients' hospital stays (ie, before discharge [baseline examination]). Follow-up data were obtained up to 1 year after the baseline examination.

Results: The mean FI-Lab score was 0.34±15, with an upper limit of 0.74. The FI-Lab was correlated with all the other frailty instruments (all $P<0.001$). The FI-Lab revealed an area under the receiver-operating characteristic curve (AUC) for 6-month and 1-year mortality of 0.765 (0.694–0.836) and 0.769 (0.706–0.833), respectively (all $P<0.001$). Each 0.01 increment in FI-Lab increased the risk (adjusted for age and sex) for 6-month and 1-year mortality by 7.2% and 7.1%, respectively (all adjusted $P<0.001$). When any of the other FIs (except the FI-combined) were also included in the models, each 0.01 increment in FI-Lab score was associated with an increase in the risk of 6-month and 1-year mortality by 4.1%–5.4% (all adjusted $P<0.001$).

Conclusion: The FI-Lab showed key characteristics of an FI. The FI-Lab can be applied as a single frailty measure or in combination with/in addition to other frailty instruments.

Keywords: older people, hospital, geriatric wards, frailty, risk stratification, mortality

Introduction

Worldwide, the older population is an ever-growing group[1,2] and represents a large proportion of individuals treated and cared for in hospitals and/or outpatient settings in many countries. Some older people are active and fit, whereas others show complex health status with diverse, adverse medical conditions (eg, malnutrition,[3,4] sarcopenia,[5] and mobility impairment[6]), chronic diseases, and/or disability. These latter individuals may be frail or at least at risk of becoming frail.[7–9] Frail older people show an increased vulnerability to stressors and have an increased risk in terms of adverse health outcomes, such as mortality.[7,10–17] Some researchers consider frailty a medical syndrome (physical and/or cognitive) focusing particularly but not exclusively on nondisabled people.[10,17,18] Others view frailty as a broadly defined state of an individual.[7–9] Nonetheless, there is overall agreement in the assumption that identification of frailty and/or its severity may aid improvements in management, decision making, and/or care planning for older people.[9,17,19–23] Frailty and its severity are considered to be excellent estimates

of an older individual's biological age, which has been found to be a better indicator of an older person's mortality risk than his or her chronological age.[24]

Among the different instruments used to evaluate frailty,[17,25–30] Fried et al's frailty phenotype[10] and Rockwood et al's[7] and Mitnitski et al's frailty index (FI)[11] are probably the best known. A limitation of the frailty phenotype is that it does not allow the grade of frailty severity to be differentiated.[31] The FI represents a quantitative measure of the health status of an individual.[32] It is the ratio of an individual's health deficits to the total number of health deficits evaluated.[7,11] Accordingly, the more health deficits an individual demonstrates, the more frail he or she is considered to be.[11] Health deficits used to construct an FI can embrace a whole range of health problems, including symptoms, signs, laboratory abnormalities, diseases, and disabilities.[9] An FI can be operationalized on the basis of different data sets,[8] eg, from data deriving from a comprehensive geriatric assessment (CGA).[33–35] A further and major strength of the FI is that it allows a fine grading of the severity of frailty.[11] The FI approach has repeatedly been found to be very powerful in identifying older people at high risk of mortality.[7,34,36,37] A limitation of the FI is that the evaluation of individuals in relation to a larger list of clinical health deficits is time-consuming.

Recently, FIs based on routine blood tests (eg, white blood-cell count, hemoglobin, sodium, potassium, creatinine, and albumin) and standard physical measures (such as blood pressure and/or pulse) (FI-Lab)[32,38,39] or at least in part on more specialized blood tests (eg, telomere length, DNA repair, and DNA repair:damage ratio) (FI-B)[40] have been introduced and evaluated in community-dwelling and/or institutionalized persons.[32,38–40] In these studies,[32,38–40] the different FI-Lab measures[32,38,39] and/or the FI-B[40] were found to be powerful predictors of mortality. An FI based solely on routine laboratory parameters for a blood and/or urine sample might be an easy and feasible frailty instrument in a busy clinical setting, thereby overcoming the aforementioned limitations of a classical FI. Abnormal results in routine blood and/or urine tests might mirror preclinical health deficits and/or acute/chronic diseases. It is thus logical to suggest that different preclinical conditions and/or diseases might contribute additively or synergistically to a person's risk of dying or suffering from other adverse health outcomes. However, until now, no study has operationalized and evaluated an FI-Lab based solely on routine blood and/or urine tests. Moreover, no study has evaluated an FI-Lab or FI-B in a cohort of hospitalized patients.

Against this background, by utilizing a reanalysis of data from a recent prospective longitudinal analysis of a cohort of hospitalized patients on geriatric wards,[12] we aimed to 1) operationalize an FI-Lab from routine laboratory parameters based on a blood and urine sample, 2) assess the relationship of the FI-Lab to other frailty instruments, and 3) investigate the predictive value of the FI-Lab in relation to 6-month and 1-year mortality compared to its individual items and other frailty instruments.

Materials and methods
Study design and study population

This study was a secondary analysis of the database from a recent prospective, longitudinal study of 307 patients hospitalized on the geriatric wards of the Geriatrics Center Erlangen, Hospital of the Congregation of St Francis Sisters of Vierzehnheiligen, Erlangen, Germany.[12] The inclusion criterion for this study was age 65 years or older. Exclusion criteria were the inability to give written informed consent or unavailability of a legal guardian to give written informed consent on behalf of the study participant. Blood and urine samples from the study participants were taken on admission, at various other time points during hospital stays, and before the patients were discharged. The blood and urine parameters assessed from samples taken from the patients before discharge were used for calculating the FI-Lab (baseline examination). In parallel, the patients were evaluated in terms of a broad spectrum of clinical characteristics (demographic data, functional impairments, diseases, Cumulative Illness Rating Scale – Geriatrics [CIRS-G], and Barthel Index, among other tools for a CGA) and different frailty instruments (a 50-item FI based on a comprehensive geriatric assessment [FI-CGA], the Clinical Frailty Scale, the rule-based frailty definition, and the frailty phenotype, among others) at the same time before discharge (baseline examination). So far, follow-up data have been obtained at 6 months and 1 year after the baseline examination. These data include information about the death of study participants during follow-up. Follow-up data were collected by using telephone interviews with patients, their physicians, specialists, relatives, or legal guardians. The study followed the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Ethics Committee of the University of Erlangen-Nuremberg. Written informed consent was obtained from each study participant or from his or her legal guardian.

FI-Lab

The FI-Lab as operationalized in this study was based on 22 routine parameters for a blood sample and one standard parameter for a spot urine sample. In selecting the individual parameters that construct the FI-Lab, care was taken that as a whole the FI-Lab captured information with respect to the

functioning/health status of different bodily/organ systems. Consequently, the FI-Lab as used in this study includes hematological, inflammatory, coagulation, electrolyte, renal, liver, and thyroid parameters. The FI was constructed by coding each variable as either 0 or 1. As such, 0 indicates that values were within the normal range or cutoffs (ie, no deficit present) and 1 that values were either above or below the normal range or cutoffs (ie, a deficit). The individual standard laboratory parameters that constitute the FI-Lab and their normal range or cutoff values are shown in Table 1. For calculation of the FI-Lab for any individual, the number of deficits was summed and divided by the number of potential deficits evaluated. Therefore, the FI-Lab for any individual resulted in a score ranging in magnitude from 0 to 1. For example, a person with a deficit in five variables and no deficits in the other 18 variables of the 23-item FI-Lab would have an FI-Lab score of 0.217 (5 divided by 23). The FI-Lab was calculated only if more than 80% of the component variables were available for a given individual.

FI-CGA

The FI-CGA was composed of up to 50 items from Rockwood et al's 52-item FI-CGA.[34] In contrast to the 52-item FI-CGA by Rockwood et al[34] the 50-item FI-CGA in the study presented here did not include the two items orthostatic hypotension and functional reach. In brief, the 50 different individual health deficits (items) used to construct the 50-item FI-CGA refer to nine different domains of a CGA[33] (cognition, emotion, communication, mobility, balance, bladder function, bowel function, nutrition, and instrumental and basic activities of daily living), several diseases related to different organ systems, systolic and diastolic blood pressure levels, self-reported quality of life, and the number of medications. Each item of the FI-CGA was scored (according to the severity of the health deficit, with a maximum score of 1 per item) according to the criteria previously described in detail in the aforementioned work by Rockwood et al.[34] The FI score was finally calculated as the score in each item divided by the total number of items evaluated, resulting in an FI-CGA score ranging in magnitude between 0 and 1.

FI-combined

The FI-combined was operationalized based on the items of the aforementioned 23-item FI-Lab and the aforementioned 50-item FI-CGA. Therefore, the FI-combined was composed of 73 items. The FI-combined was calculated as the score in each item divided by the total number of items evaluated, resulting in an FI-combined score between 0 and 1.

Table 1 Standard laboratory parameters used to construct the frailty index based on routine blood and urine tests (FI-Lab)

Standard laboratory parameter	Normal range/cutoff	AUC (95% CI) for 6-month mortality	*P*-value	AUC (95% CI) for 1-year mortality	*P*-value
Blood sample					
White blood cells (number/μL)	4,000–10,000	0.592 (0.498–0.686)	0.045	0.589 (0.505–0.673)	0.03
Red blood cells (number/μL)	Men 4.5×10^6–5.9×10^6, women 3.9×10^6–5.1×10^6	0.53 (0.441–0.618)	0.519	0.546 (0.466–0.625)	0.269
Hemoglobin (g/dL)	Men 14–17.5, women 12.3–15.3	0.579 (0.496–0.662)	0.085	0.592 (0.518–0.666)	0.025
MCV (fL)	80–96	0.492 (0.402–0.582)	0.865	0.517 (0.435–0.599)	0.674
Hematocrit (%)	Men 40–52, women 35–47	0.613 (0.526–0.699)	0.014	0.614 (0.536–0.692)	0.006
Platelets (number/μL)	150,000–400,000	0.476 (0.379–0.572)	0.6	0.471 (0.384–0.558)	0.478
Quick value (%)	70–130	0.562 (0.469–0.654)	0.179	0.54 (0.458–0.622)	0.332
PTT (seconds)	25.1–36.5	0.597 (0.506–0.689)	0.034	0.589 (0.506–0.672)	0.032
Sodium (mval/L)	136–145	0.562 (0.47–0.655)	0.176	0.566 (0.483–0.649)	0.109
Potassium (mg/dL)	3.5–5.1	0.561 (0.466–0.656)	0.183	0.535 (0.452–0.618)	0.39
Calcium (mval/L)	4.3–5.2	0.647 (0.555–0.74)	0.001	0.617 (0.534–0.7)	0.005
Protein, total (g/dL)	6.4–8.7	0.548 (0.457–0.638)	0.305	0.568 (0.487–0.648)	0.103
Urea (mg/dL)	17–43	0.572 (0.483–0.661)	0.116	0.564 (0.483–0.644)	0.122
Creatinine (mg/dL)	Men 0.7–1.2, women 0.5–0.9	0.504 (0.415–0.594)	0.922	0.517 (0.436–0.597)	0.687
Bilirubin (mg/dL)	<1	0.558 (0.463–0.653)	0.207	0.548 (0.464–0.632)	0.248
AST (SGOT, U/L)	Men <35, women <31	0.571 (0.477–0.665)	0.123	0.573 (0.489–0.657)	0.076
ALT (SGPT, U/L)	Men <45, women <34	0.55 (0.456–0.644)	0.272	0.548 (0.464–0.631)	0.248
GGT (U/L)	Men <55, women <33	0.58 (0.495–0.665)	0.081	0.59 (0.513–0.666)	0.03
LDH (U/L)	Men <248, women <247	0.609 (0.52–0.699)	0.018	0.637 (0.559–0.716)	0.001
Albumin (g/dL)	3.97–4.94	0.612 (0.53–0.693)	0.015	0.606 (0.531–0.681)	0.01
CRP (mg/dL)	<0.5	0.623 (0.545–0.702)	0.007	0.601 (0.527–0.676)	0.014
TSH (μU/mL)	0.27–4.2	0.489 (0.4–0.578)	0.817	0.496 (0.415–0.576)	0.916
Spot urine					
Protein, total (mg/dL)	<15 mg/dL	0.591 (0.495–0.686)	0.051	0.576 (0.492–0.661)	0.066

Abbreviations: AUC, area under the receiver-operating characteristic curve; CI, confidence interval; MCV, mean corpuscular volume; PTT, partial thromboplastin time; TSH, thyroid-stimulating hormone; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; ALT, alanine aminotransferase; SGPT, serum glutamic pyruvic transaminase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; CRP, C-reactive proteine.

Clinical Frailty Scale

The Clinical Frailty Scale consists of nine different categories, and grades individuals along a very fit (category 1) to terminally ill (category 9) continuum.[17] The Clinical Frailty Scale is based on clinical judgment to interpret the results of history-taking and clinical examination. It takes physical activity, quality of disease control, functioning in instrumental and basic activities of daily living, history and severity of dementia, and the presence of terminal illnesses into account.[17]

Rule-based frailty definition

The four-level rule-based frailty definition was constructed as previously described in detail by Rockwood et al.[41] It classifies persons in terms of frailty on a 4-point scale: level 0 (fit) to level 3 (frail), based on ability to walk, perform basic activities of daily living (eating, dressing, bathing, bed transfer), bowel function, bladder function, cognitive function, and the presence/absence of dementia.[41]

Frailty phenotype

The frailty phenotype is based on five phenotypic criteria (shrinking, ie, weight loss [unintentional]/loss of muscle mass, poor endurance/exhaustion, slowness, low physical activity, and muscle weakness).[10] In the current study, the phenotypic criteria of the frailty phenotype were operationalized as described in detail elsewhere.[36] Patients who revealed none of the phenotypic criteria were considered to be robust, those with one or two to be "prefrail", and those with three or more to be frail.[36]

Statistics

All statistical analyses were performed using SPSS software (IBM Corporation, Armonk, NY, USA). Results are expressed as mean ± standard deviation, median (interquartile range), or percentages. Comparison between patients stratified according to different FI-Lab scores were performed using χ^2 tests. Correlation analyses were performed using Spearman's ρ. Partial-correlation analyses were performed to evaluate the relationship between the FI-Lab and the other frailty instruments, taking potential confounders, ie, age and sex, into account. A correlation coefficient r or partial r of 0.9–1 indicates "very high", 0.7–0.9 "high", 0.5–0.7 "moderate", 0.3–0.5 "low", and 0–0.3 "negligible" correlation.[42] The various frailty instruments were analyzed as continuous variables, unless otherwise indicated. Receiver-operating characteristic curves were calculated to estimate area under the receiver-operating characteristic curve (AUCs) for the different items and frailty instruments in relation to mortality. AUC values >0.9 indicate "very good", >0.8 "good", and >0.7 "useful" predictive ability of the model.[43] An AUC value of 0.5 indicates that the predictive ability of the model is not better than chance.[43] Comparisons among the AUCs were performed using the method of Hanley and McNeil.[44] Kaplan–Meier estimates were used to determine whether different patients with different FI-Lab scores differed in their ability to predict 6-month and 1-year mortality. The *P*-value reported for the difference with reference to mortality among the patient groups with different FI-Lab scores was based on the log-rank test. Cox proportional hazard models were used to estimate the probability of survival, in which FI-Lab, FI-CGA, and FI-combined values were converted to 0–100 integers by rounding them after multiplying them by 100, giving equal percentage increments for modeling. Hazard ratios (HRs) of the FI-Lab and the other frailty instruments were adjusted for age and sex, among other variables, and were considered both separately and together. The level of statistical significance was set a priori at $P<0.050$.

Results

For 306 of the 307 patients, more than 80% of the laboratory parameters that comprise the FI-Lab were available. The patient with an availability of less than 80% of the laboratory parameters comprising the FI-Lab was excluded from the analysis. This person was an 87-year-old male who had a body mass index (BMI) of 28 kg/m², a Mini-Mental State Examination (MMSE) score of 70 points, a Barthel Index score of 70 points, and a CIRS-G score of 22 points before discharge (at the baseline examination). Follow-up data at 6-month follow-up were available from all the remaining 306 study participants; 47 of these (15.4%) had died by that point. Follow-up data at 1 year were not available for two patients of the aforementioned 306 study participants. The two patients for whom no follow-up data were available at 1 year were 89±4.2 years old, one woman and one man, had a BMI of 30.7±8.8 kg/m², an MMSE score of 27.5±0.7 points, a Barthel Index score of 70±7.1, CIRS-G score of 10±2.8 points, and an FI-Lab score of 0.28±0.2 before discharge (at the baseline examination). Of the remaining 304 patients for whom follow-up data were available at 1 year of follow-up, 62 patients (20.4%) had died by that point.

The 306 patients for whom more than 80% of the laboratory parameters that constitute the FI-Lab were available were 82.9±6.4 years old, 67.6% female, 163±9.7 cm tall, weighed 73.2±16 kg, with BMI scores of 27.5±5.6 kg/m²;

25.8% had weight loss >4.5 kg in the previous year, MMSE scores were 25.5±4.6 points, Geriatric Depression Scale scores were 3.88±2.7 points, 63.7% had timed "up and go" (TUG) results >19 seconds or were unable to perform the TUG, Barthel Index scores were 70.1±21 points, CIRS-G scores were 17.4±5.6 points; and 47.4% had a history of heart failure, 13.7% myocardial infarction, 17.6% peripheral vascular disease, 20.3% stroke, 14.7% cancer, 37.9% diabetes mellitus, 16.7% lung disease, 64.7% kidney disease, 23.5% urinary incontinence or catheterized, 31.7% constipation, 96.1% received more than five medications, and 16% were institutionalized. The clinical characteristics and scores of the different frailty instruments of these aforementioned patients stratified according to the different FI-Lab scores are given in Table 2. Patients with higher FI-Lab scores included a greater percentage of male patients, patients with weight loss >4.5 kg in the last year, those with lower MMSE scores, a greater percentage of patients with a TUG >19 seconds or unable to perform the TUG, a greater comorbidity burden as assessed by the CIRS-G, a greater percentage of patients with heart failure, peripheral vascular disease, kidney disease, urinary incontinence or catheterized, constipation, more than five medications, FI-CGA scores, FI-combined scores, Clinical Frailty Scale categories, rule-based frailty-definition level, frail state (three or more phenotypic components) according to the frailty phenotype, and higher 6-month and 1-year mortality compared to patients with lower FI-Lab scores.

FI-Lab scores showed normal distribution. The mean FI-Lab score was 0.34±0.15, and the median 0.34 (0.22–0.43). The minimum FI-Lab score observed was 0, while the maximum was 0.74. The first, fifth, 95th, and 99th percentiles of the FI-Lab were 0.04, 0.09, 0.57, and 0.7, respectively. Univariate correlation analysis revealed relationships between the FI-Lab and the FI-CGA, FI-combined, Clinical Frailty Scale, rule-based frailty definition, and frailty phenotype ($r=0.497$ [$P<0.001$], $r=0.739$ [$P<0.001$], $r=0.483$ [$P<0.001$], $r=0.37$ [$P<0.001$], and $r=0.4$ [$P<0.001$], respectively). Relationships between the FI-Lab and the FI-CGA, FI-combined, Clinical Frailty Scale, rule-based frailty definition, and frailty phenotype were independent of age and sex (partial $r=0.478$ [adjusted $P<0.001$], partial $r=0.734$ [adjusted $P<0.001$], partial $r=0.458$ [adjusted $P<0.001$], partial $r=0.355$ [adjusted $P<0.001$], and partial $r=0.376$ [adjusted $P<0.001$], respectively).

The FI-Lab revealed at least useful discriminative accuracy (ie, AUC >0.7) for 6-month and 1-year mortality (Table 3). Several individual items of the FI-Lab, ie, white blood cells, hemoglobin, hematocrit, partial thromboplastin time, calcium, GGT, LDH, albumin, and CRP were able to discriminate between patients who had died and those who had not during the 6-month and/or 1-year follow-up periods (Table 1). However, when considered individually, the items of the FI-Lab had rather poor discriminative accuracy (Table 1). The discriminative accuracy of the FI-Lab for 6-month and 1-year mortality was greater than any individual item of the FI-Lab (all $P<0.05$).

In addition to the FI-Lab, all the other frailty instruments evaluated in this study were also able to discriminate between patients who had died and those who were alive at 6-month and 1-year follow-ups (Table 3). The discriminative accuracy of the FI-Lab for 6-month mortality was inferior compared to the FI-CGA, FI-combined, and the Clinical Frailty Scale (all $P<0.05$, Table 3) and similar compared to the rule-based frailty definition and the frailty phenotype (both $P\geq0.05$, Table 3). The discriminative accuracy of the FI-Lab for 1-year mortality was inferior to the FI-combined and the Clinical Frailty Scale (all $P<0.05$, Table 3), similar to the FI-CGA and the frailty phenotype (both $P\geq0.05$, Table 3), and superior to the rule-based frailty definition ($P<0.05$, Table 3).

Unadjusted and adjusted HRs for each increment in category/level or 0.01 increments in score of the different frailty instruments are given in Table 4. Each 1% increase in FI-Lab scores (each 0.01 increment) increased HRs for 6-month and 1-year mortality by 7.2% and 7.1%, respectively (Table 4). In an age- and sex-adjusted model, each 0.01 increment in FI-Lab score increased HRs for 6-month and 1-year mortality by 7.2% and 7.1%, respectively (Table 4). When the FI-CGA, Clinical Frailty Scale, rule-based frailty definition, or frailty phenotype were also entered into the models, each 0.01 increment in FI-Lab score still showed HRs for 6-month and 1-year mortality of 4.1%–5.4% (Table 5).

Discussion

We operationalized an FI-Lab from 22 routine laboratory parameters based on a blood sample and one standard parameter based on a urine sample in 306 hospitalized patients on geriatric wards. Howlett et al[32] and Rockwood et al[38] evaluated a 23-item FI-Lab, which was based on 21 routine blood tests plus standard physical measures (ie, systolic and diastolic blood pressure),[32,38] in community-dwelling older people and/or institutionalized individuals. Similarly, Blodgett et al[39] evaluated a 23-item FI-Lab, which was constructed by routine blood tests plus standard physical measures (ie, blood pressure and pulse), in community-dwelling older men. Mitnitski et al[40] evaluated an FI-B based

Table 2 Clinical characteristics (baseline examination), 6-month mortality, and 1-year mortality of study participants according to frailty index based on routine blood and urine tests (FI-Lab) score

Clinical characteristic	Score 0 (n=2)	Score 0.001–0.1 (n=21)	Score 0.101–0.2 (n=33)	Score 0.201–0.3 (n=51)	Score 0.301–0.4 (n=89)	Score 0.401–0.5 (n=70)	Score 0.501–0.6 (n=28)	Score 0.601–0.7 (n=10)	Score >0.7 (n=2)	P-value
Age (years)	81±2.8	84.5±6.4	81.8±5.3	82.2±6.6	83±6.6	83.6±7	82.1±5.2	84±6.2	79.5±6.4	0.901
Female, % (n)	100 (2)	90.5 (19)	84.8 (28)	76.5 (39)	61.8 (55)	60 (42)	53.6 (15)	70 (7)	0	0.004
Height (cm)	159±5.7	159±8.1	162±7.1	163±8.7	164±9.5	164±11	165±12	159±11	172±5.7	0.404
Weight (kg)	79±21	72.3±13	70.4±16	70.4±15	75.6±17	71.9±15	79.9±19	65.1±11	88.2±13	0.216
BMI (kg/m²)	31±6	28.6±5.3	26.7±5.2	26.6±5.5	28.1±6.1	26.9±5.4	29.4±5.8	25.7±1.6	29.7±2.3	0.437
Weight loss >4.5 kg in last year (unintentional), % (n)	0	28.6 (6)	12.1 (4)	15.7 (8)	20.2 (18)	40 (28)	39.3 (11)	40 (4)	0	0.011
MMSE (points)	28.5±0.7 (n=2)	26.5±3.8 (n=21)	26.3±2.7 (n=33)	25.5±4.6 (n=47)	25.9±4.6 (n=89)	24.8±4.5 (n=70)	25.2±4.2 (n=26)	21.3±9 (n=10)	26±0 (n=2)	0.005
GDS (points)	2.5±2.1 (n=2)	3.1±2.1 (n=21)	4.12±2.9 (n=33)	3.98±3.1 (n=47)	4.1±2.8 (n=89)	3.71±2.6 (n=68)	4.08±2.3 (n=26)	3.7±1.4 (n=10)	1.5±2.1 (n=2)	0.941
TUG >19 seconds or unable to perform TUG, % (n)	50 (1)	47.6 (10)	45.5 (15)	52.9 (27)	59.6 (53)	77.1 (54)	85.7 (24)	90 (9)	100 (2)	0.001
Barthel Index (points)	75±28	83.6±12	79.4±16	73.5±23	69.8±21	66.1±19	61.6±24	51±25	52.5±11	0.429
CIRS-G (points)	9±2.8	13.2±3.7	13.8±4.9	15.4±5	18.3±5.6	19.2±5	19.1±4.3	23.1±4.3	28.5±0.7	<0.001
Heart failure, % (n)	0	28.6 (6)	24.2 (8)	39.2 (20)	50.6 (45)	55.7 (39)	67.9 (19)	70 (7)	50 (1)	0.004
Myocardial infarction, % (n)	0	9.5 (2)	9.1 (3)	11.8 (6)	13.5 (12)	18.6 (13)	7.1 (2)	30 (3)	50 (1)	0.407
Peripheral vascular disease, % (n)	0	23.8 (5)	9.1 (3)	2 (1)	19.1 (17)	24.3 (17)	28.6 (8)	30 (3)	0	0.027
Stroke, % (n)	0	4.8 (1)	21.2 (7)	35.3 (18)	22.5 (20)	14.3 (10)	10.7 (3)	20 (2)	50 (1)	0.054
Cancer, % (n)	0	9.5 (2)	15.2 (5)	5.9 (3)	15.7 (14)	17.1 (12)	21.4 (6)	20 (2)	50 (1)	0.475
Diabetes mellitus, % (n)	50 (1)	28.6 (6)	27.3 (9)	29.4 (15)	39.3 (35)	48.6 (34)	42.9 (12)	30 (3)	50 (1)	0.415
Lung disease, % (n)	0	23.8 (5)	15.2 (5)	19.6 (10)	21.3 (19)	12.9 (9)	10.7 (3)	0	0	0.559
Kidney disease, % (n)	0	42.9 (9)	45.5 (15)	43.1 (22)	71.9 (64)	84.3 (59)	64.3 (18)	90 (9)	100 (2)	<0.001
Urinary incontinence or catheterized, % (n)	50 (1)	4.8 (1)	6.1 (2)	15.7 (8)	21.3 (19)	34.3 (24)	39.3 (11)	40 (4)	100 (2)	<0.001
Constipation, % (n)	50 (1)	28.6 (6)	21.2 (7)	39.2 (20)	19.1 (17)	42.9 (30)	42.9 (12)	30 (3)	50 (1)	0.044
>5 medications, % (n)	50 (1)	95.2 (20)	93.9 (31)	92.2 (47)	96.6 (86)	98.6 (69)	100 (28)	100 (10)	100 (2)	0.034
Institutionalized, % (n)	0	4.8 (1)	9.1 (3)	21.6 (11)	18 (16)	15.7 (11)	21.4 (6)	10 (1)	0	0.622
FI-Lab (−)	0±0	0.07±0	0.15±0	0.24±0	0.35±0	0.45±0	0.53±0	0.63±0	0.74±0	<0.001
FI-CGA (−)	0.25±0.2	0.29±0.1	0.29±0.1	0.34±0.1	0.39±0.1	0.44±0.1	0.49±0.1	0.51±0.1	0.57±0.1	0.015
FI-combined (−)	0.17±0.2	0.23±0.1	0.24±0.1	0.31±0.1	0.37±0.1	0.45±0.1	0.5±0.1	0.55±0.1	0.63±0	<0.001
Clinical Frailty Scale (category)	4.5±2.1	4.43±0.9	4.52±1.1	4.98±1.4	5.38±1.2	5.97±1.3	6.61±1.4	6.4±0.7	0.65±0.7	<0.001
Rule-based frailty definition (level)	1±1.4	1.05±1.2	1.03±1.1	1.25±1.2	1.63±1.2	1.99±0.9	2.21±0.9	2.5±1	2.5±0.7	0.001
Frail state (≥3 phenotypic components) according to frailty phenotype, % (n)	50 (1)	23.8 (5)	21.2 (7)	29.4 (15)	39.3 (35)	52.9 (37)	75 (21)	100 (10)	100 (2)	<0.001
Six-month mortality, % (n)	0	0	3 (1)	7.8 (4)	9 (8)	25.7 (18)	35.7 (10)	40 (4)	100 (2)	<0.001
One-year mortality, % (n)	0	0	3.1 (1)	13.7 (7)	12.5 (11)	32.9 (23)	46.3 (13)	50 (5)	100 (2)	<0.001

Note: The data are presented as mean ± standard deviation unless otherwise indicated.
Abbreviations: BMI, body mass index; CGA, comprehensive geriatric assessment; CIRS-G, Cumulative Illness Rating Scale – geriatric; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; TUG, timed "up and go".

Table 3 Ability of different frailty instruments and comparison of frailty index based on routine blood and urine tests (FI-Lab) with other frailty instruments to predict 6-month and 1-year mortality

Frailty instrument	AUC (95% CI) for 6-month mortality (n=306)	P-value	P-value, AUC 1 vs AUCs 2–7	AUC (95% CI) for 1-year mortality (n=304)	P-value	P-value, AUC 1 vs AUCs 2–7
FI-Lab	0.765 (0.694–0.836)	<0.001	–	0.769 (0.706–0.833)	<0.001	–
FI-CGA	0.834 (0.767–0.901)	<0.001	0.030	0.806 (0.744–0.867)	<0.001	0.139
FI-combined	0.853 (0.792–0.915)	<0.001	<0.001	0.832 (0.776–0.888)	<0.001	0.004
Clinical Frailty Scale	0.867 (0.807–0.926)	<0.001	0.002	0.852 (0.8–0.904)	<0.001	0.005
Rule-based frailty definition	0.716 (0.642–0.79)	<0.001	0.126	0.703 (0.638–0.769)	<0.001	0.040
Frailty phenotype	0.754 (0.687–0.82)	<0.001	0.391	0.724 (0.659–0.79)	<0.001	0.118

Abbreviations: AUC, area under the receiver-operating characteristic curve; CGA, comprehensive geriatric assessment; CI, confidence interval.

on 40 biomarkers that included at least in part more special blood tests (eg, cytomegalovirus serology [IgG], senescent memory CD4 T cells, telomere length, DNA repair, DNA damage:repair ratio, and mitochondrial DNA haplogroup) in a population-based cohort of individuals aged 85 years or older. As operationalized in our current study, the FI-Lab differs from the aforementioned FI-Labs[32,38,39] and the aforementioned FI-B by Mitnitski et al.[40] In contrast to the different FI-Labs of the aforementioned authors,[32,38,39] no standard physical measures (such as blood pressure and/or pulse) were included to operationalize the FI-Lab in the study presented here. In addition, at least some routine blood tests used to construct FI-Lab differed between the FI-Labs of the aforementioned authors[32,38,39] and the FI-Lab in our current study. In contrast to the FI-B of Mitnitski et al,[40] only routine laboratory blood parameters and no more special blood tests were used to operationalize the FI-Lab presented here. One strength of the FI-Lab, as operationalized in our current study, is that it can be analyzed from a single laboratory report from

a general laboratory without the need for consideration of additional parameters, such as standard physical tests or more specialized blood tests.

The FI-Lab evaluated in our study showed valuable discriminatory accuracy, as indicated by an AUC >0.70 for 6-month and 1-year mortality. Clearly, abnormalities in routine blood and/or urine parameters might reflect subclinical organ changes, adverse medical conditions, and/or acute or chronic diseases that potentially impact on an older person's mortality risk. In addition, an interaction between chronic diseases and functional impairments that impact on the mortality risk of older persons has been previously reported by other authors.[45–47] Therefore, several of the aforementioned conditions might have driven the predictive power of the FI-Lab in our current study. Patients with higher FI-Lab scores showed a greater overall comorbidity burden, as indicated by higher CIRS-G score and a greater percentage of patients with heart failure, peripheral vascular disease, kidney disease, urinary incontinence or catheterized, constipation,

Table 4 HRs and adjusted (for age and sex) HRs for each increment in category or score of 0.01 of the different frailty instruments in relation to 6-month and 1-year mortality

Frailty instrument	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Six-month mortality				
FI-Lab (per each 0.01 increment in score)	1.072 (1.048–1.096)	<0.001	1.072 (1.048–1.097)	<0.001
FI-CGA (per each 0.01 increment in score)	1.105 (1.076–1.135)	<0.001	1.102 (1.073–1.132)	<0.001
FI-combined (per each 0.01 increment in score)	1.134 (1.099–1.171)	<0.001	1.133 (1.098–1.17)	<0.001
Clinical Frailty Scale (per each increment in category [1–9])	2.614 (2.132–3.206)	<0.001	2.545 (2.055–3.15)	<0.001
Rule-based frailty definition (per each increment in level [0–3])	2.333 (1.613–3.373)	<0.001	2.259 (1.554–3.285)	<0.001
Frailty phenotype (per increase in category [robust/prefrail/frail])	6.063 (2.983–12.325)	<0.001	5.618 (2.754–11.46)	<0.001
One-year mortality				
FI-Lab (per each 0.01 increment in score)	1.071 (1.05–1.092)	<0.001	1.071 (1.05–1.093)	<0.001
50-item FI-CGA (per each 0.01 increment in score)	1.089 (1.066–1.113)	<0.001	1.087 (1.064–1.112)	<0.001
FI-combined (per each 0.01 increment in score)	1.119 (1.09–1.148)	<0.001	1.118 (1.088–1.148)	<0.001
Clinical Frailty Scale (per each increment in category [1–9])	2.569 (2.128–3.1)	<0.001	2.515 (2.069–3.059)	<0.001
Rule-based frailty definition (per each increment in level [0–3])	2.189 (1.611–2.975)	<0.001	2.142 (1.567–2.929)	<0.001
Frailty phenotype (per increase in category [robust/prefrail/frail])	3.977 (2.389–6.622)	<0.001	3.744 (2.241–6.257)	<0.001

Abbreviations: CGA, comprehensive geriatric assessment; CI, confidence interval; FI-Lab, frailty index (based on routine blood and urine tests); HR, hazard ratio.

Table 5 Adjusted HRs for age, sex, and each increment in category/level or score of 0.01 of the frailty index based on FI-Lab, FI-CGA, rule-based frailty definition, and frailty phenotype in relation to 6-month and 1-year mortality

Variable	Adjusted HR (95% CI)	*P*-value
Six-month mortality		
Age	1.026 (0.974–1.081)	0.329
Sex	0.747 (0.418–1.333)	0.324
FI-Lab (per each 0.01 increment in score)	1.046 (1.02–1.073)	0.001
Clinical Frailty Scale (per each increment in category [1–9])	2.287 (1.83–2.858)	<0.001
Age	1.046 (0.995–1.099)	0.077
Sex	0.711 (0.399–1.269)	0.249
FI-Lab (per each 0.01 increment in score)	1.041 (1.017–1.066)	0.001
FI-CGA (per each 0.01 increment in score)	1.087 (1.056–1.119)	<0.001
Age	1.064 (1.01–1.12)	0.019
Sex	0.693 (0.387–1.241)	0.217
FI-Lab (per each 0.01 increment in score)	1.054 (1.028–1.08)	<0.001
Rule-based frailty definition (per each increment in level [0–3])	3.562 (1.915–6.627)	<0.001
Age	1.052 (1.001–1.107)	0.047
Sex	0.716 (0.402–1.275)	0.257
FI-Lab (per each 0.01 increment in score)	1.051 (1.026–1.076)	<0.001
Frailty phenotype (per increase in category [robust/prefrail/frail])	3.869 (1.852–8.085)	<0.001
One-year mortality		
Age	1.027 (0.974–1.082)	0.322
Sex	0.745 (0.417–1.33)	0.319
FI-Lab (per each 0.01 increment in score)	1.046 (1.02–1.073)	0.001
Clinical Frailty Scale (per each increment in category [1–9])	2.282 (1.826–2.852)	<0.001
Age	1.046 (0.995–1.099)	0.076
Sex	0.711 (0.398–1.268)	0.248
FI-Lab (per each 0.01 increment in score)	1.041 (1.017–1.066)	0.001
FI-CGA (per each 0.01 increment in score)	1.087 (1.056–1.119)	<0.001
Age	1.065 (1.011–1.121)	0.018
Sex	0.69 (0.385–1.236)	0.212
FI-Lab (per each 0.01 increment in score)	1.053 (1.027–1.079)	<0.001
Rule-based frailty definition (per each increment in level [0–3])	3.558 (1.913–6.616)	<0.001
Age	1.053 (1.001–1.108)	<0.045
Sex	0.713 (0.4–1.271)	0.251
FI-Lab (per each 0.01 increment in score)	1.05 (1.026–1.075)	<0.001
Frailty phenotype (per increase in category [robust/prefrail/frail])	3.828 (1.835–7.985)	<0.001

Abbreviations: CGA, comprehensive geriatric assessment; CI, confidence interval; FI-Lab, frailty index (based on routine blood and urine tests); HR, hazard ratio.

polypharmacy (more than five medications), lower cognitive function (lower MMSE score), mobility impairment (TUG >19 seconds or unable to perform the TUG), and weight loss >4.5 kg in the last year compared to patients with lower FI-Lab scores. In accordance with the findings of this study, in studies by other authors, the comorbidity burden as assessed by the CIRS-G,[48,49] heart failure,[50] peripheral vascular disease,[51] kidney disease,[52] impairment in bladder function,[53,54] constipation,[55] polypharmacy,[56] impairment in cognition,[57,58] mobility impairment,[59,60] and weight loss[61] were found to be associated with a greater mortality risk in older people. In addition, in the study presented here, patients with higher FI-Lab scores included more male than female patients compared to patients with lower FI-Lab scores. In previous

studies on older individuals,[55,62] a greater risk for mortality in males than females was found. However, it is worth noting that in our study, the predictive power of the FI-Lab was found to be independent of the sex of the patients.

The FI-Lab evaluated here showed a fine grading of the patients' 6-month and 1-year mortality risk independently of age and sex. In line with our findings, such a fine grading of patient-mortality risk has also been found previously with an FI.[7,63] Of interest, the risk for 6-month and 1-year mortality captured by the FI-Lab, as indicated by the HR, was independent of that of the Clinical Frailty Scale, FI-CGA, rule-based frailty definition, or the frailty phenotype. Consequently, the FI-Lab might be of additional value in terms of any of the other aforementioned frailty instruments when applied

to evaluate a person's mortality risk. Concordant with this, Rockwood et al[38] detected prognostic significance in relation to 6-year mortality with a 23-item FI-Lab based on standard parameters of a blood sample plus blood pressure levels that was independent of age, sex, and a 58-item clinical FI in a cohort of institutionalized older persons.

The FI-Lab differed at least in part in its accuracy to predict 6-month and/or 1-year mortality compared to other frailty instruments that were evaluated in this study. The FI-Lab showed superior discriminative accuracy for mortality to the rule-based frailty definition (for 1-year mortality), similar discriminative accuracy for mortality to the FI-CGA (for 1-year mortality), the frailty phenotype (for 6-month and 1-year mortality), and the rule-based frailty definition (for 6-month mortality), and inferior discriminative accuracy for mortality to the FI-CGA (for 6-month mortality), FI-combined (for 6-month and 1-year mortality) and Clinical Frailty Scale (for 6-month and 1-year mortality). The inferior ability of the FI-Lab to predict 6-month and/or 1-year mortality compared to some of the aforementioned frailty instruments might be due to the fact that routine blood and urine samples in general include only a smaller list of basic laboratory parameters. Consideration of a larger list of blood and urine parameters, which together capture more information with respect to the functioning/health status of different bodily/organ systems, would probably improve estimation of mortality by applying an FI-Lab. This issue should be addressed in future studies. Of note, Howlett et al[32] reported similar discriminative accuracy for 6-year mortality for their 23-item FI-Lab constructed by using standard laboratory parameters of a blood sample plus blood pressure levels and a 38-item FI based on clinical parameters in older community-dwelling or institutionalized people. In Mitnitski et al,[40] the discriminative accuracy of a 40-item FI-B constructed by using standard biomarkers and more special laboratory parameters based on a blood sample for 7-year mortality did not differ (in terms of statistical significance) compared to a 40-item FI based on clinical parameters and the frailty phenotype in a population-based sample of individuals aged 85 years or older. However, it should be taken into account that the follow-up periods of these studies were substantially longer compared to the follow-up periods of our current study.

The discriminative accuracy for 6-month and 1-year mortality of the FI-Lab evaluated in this study was superior to the discriminative accuracy of its individual items. The individual items of the FI-Lab that showed discriminative accuracy for 6-month and/or 1-year mortality included white blood cells, hemoglobin, hematocrit, partial thromboplastin time,

calcium, GGT, LDH, albumin, and CRP. In accordance with the findings of this study, individual abnormal standard blood parameters have previously been found to predict mortality. Mitnitski et al[40] reported a predictive value for 7-year mortality of abnormal white blood-cell count, hemoglobin, albumin, and highly sensitive CRP in a community-based cohort of people aged 85 years or older. With respect to abnormal albumin levels, hypoalbuminemia is a well-established prognostic marker for increased mortality risk in older people.[64] Koehler et al[65] detected an association between abnormal GGT values and mortality in older people. Wulaningsih et al[66] and Liu et al[67] found that increased serum LDH values predicted mortality.

The FI-Lab correlated with the other frailty instruments evaluated in this study independently of age and sex. Therefore, a substantial proportion of the patients in our cohort with greater frailty severity according to the FI-Lab also revealed greater frailty severity or at least a frail state according to the other frailty instruments and vice versa. In line, Rockwood et al[38] detected a relationship between a 23-item FI-Lab constructed by using standard parameters of a blood sample plus blood pressure levels and a 58-item FI based on clinical parameters in a cohort of institutionalized older people. Similarly, Mitnitski et al[40] observed a relationship between a 40-item FI-B made up of multiple biomarkers, including several that went beyond standard laboratory tests from a blood sample and a 40-item FI based on clinical parameters in a population-based sample of people 85 years or older.

The frequency distribution of the FI-Lab showed a maximum FI-Lab score of 0.74. This is in accordance with an upper limit to frailty for an FI score of approximately 0.7. Such an upper limit to frailty for an FI score of approximately 0.7 has frequently been detected in different study populations where an FI was applied.[34,36,68,69]

In 2013, a consensus document[17] was published that focused on a specific construct of frailty, ie, physical frailty. It was noted and emphasized that a broader construct of frailty and the construct of physical frailty should be conceived.[17] In this consensus document[17] work by Rockwood et al[7] has been referenced as an example for the broader construct of frailty. The theoretical background to the frailty approach by Rockwood and Mitnitski is described in detail elsewhere.[8,9] In brief, Rockwood and Mitnitski focused on the overall health state of a person as a measure of frailty.[8] This frailty approach does not exclude per se the mention and/or consideration of disability.[8] This is due to the notion that a great proportion of people who are frequently frail also show at least some degree of disability.[8] In addition, the presence of

a disability is frequently associated with increased mortality risk in older persons.[8] Considering disability among other parameters thus seems appropriate in light of graded frailty severity and mortality risk in older people.[8] In contrast to the broader construct of frailty, the construct of physical frailty targets "predisabled" people in particular (but not exclusively).[17] Moreover, and of note, disability is being considered an outcome of the construct of physical frailty.[17] Patients hospitalized on geriatric wards frequently show at least some disabilities.[70,71] This was also the case in a large proportion of the study participants in our current study. In this light, we consider the broader construct of frailty in accordance with the approach by Rockwood et al[7–9] as the very definition of frailty in the study presented here and as the conceptual frame in which this work is being developed.

This study has some major strengths. To the best of our knowledge, this is the first study to have evaluated an FI-Lab based solely on routine laboratory parameters of a blood and/or urine sample. In addition, this is the first study to evaluate an FI-Lab in a cohort of hospitalized patients. Moreover, we analyzed the predictive power of the FI-Lab for 6-month and 1-year mortality compared to its individual items and other frailty instruments. The prognostic power of a frailty instrument in relation to mortality might vary between different follow-up periods, in particular where the frailty instrument is based on items that reflect not only clinical but also subclinical deficits, such as the FI-Lab in our study.

This study has some limitations. The FI-Lab and the other frailty instruments were operationalized based on parameters that were evaluated at the end of the hospital stays of the study participants, ie, before discharge. At the end of the study participants' hospital stays, the acute diseases or exacerbations of chronic diseases that resulted in admission to hospital had been treated and controlled. The analysis of the patients in relation to frailty after treatment and control of acute diseases and exacerbations of chronic diseases might enable a more objective evaluation of the patients in relation to frailty and its severity according to the aforementioned frailty instruments than applying these tools in situations in which patients suffer from acute diseases or exacerbations of chronic diseases. Acute diseases or exacerbations of chronic disease might impact on laboratory, clinical, and functional parameters. Accordingly, it might be misleading to extrapolate the findings of our current study to patients in a situation in which they suffer from acute diseases and/or exacerbations of chronic diseases at the beginning of their hospital stays at geriatric wards. In relation to the frailty phenotype, in the study presented here, as well as other

studies,[72,73] the operationalization of the phenotypic components used differed slightly from the original operationalization by Fried et al.[10] This might have reduced the ability of the frailty phenotype in our study to predict 6-month and 1-year mortality. All the study participants were treated and cared for on geriatric wards. Extrapolation of the findings of the study presented here to other patients groups or clinical settings might thus be misleading.

Conclusion

In our study of 306 patients hospitalized on geriatric wards, an FI-Lab based solely on 23 routine laboratory parameters from blood and urine samples was associated with useful discriminative accuracy (AUC >0.7) and graded risk of 6-month and 1-year mortality. The predictive power of the FI-Lab for 6-month and 1-year mortality was independent of age, sex, and other frailty instruments. Frailty severity evaluated by FI-Lab was related to frailty status or severity assessed by other frailty instruments. The upper limit of the FI-Lab score in this study is in line with an upper limit of an FI of approximately 0.7. Accordingly, the FI-Lab showed key characteristics of an FI. The FI-Lab, used as a single tool or in combination with/in addition to other frailty measures, emerged as a valuable frailty instrument for the estimation of mortality risk of patients hospitalized on geriatric wards.

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