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DEVELOPMENT AND VALIDATION OF A TOOL TO SCREEN FOR COGNITIVE FRAILTY AMONG COMMUNITY-DWELLING ELDERS

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Abstract: *Objectives:* Reciprocal age-related impairments in physical and cognitive functioning have been termed 'cognitive frailty', which is associated with adverse health outcomes and is a potential target for preventing or delaying the onset of disability in older people. However, cognitive frailty as currently defined is challenging to diagnose. To facilitate earlier diagnosis and intervention, we conducted this study to develop and validate a simple evidence-based instrument to identify community-dwelling elders at risk of cognitive frailty. *Design:* Retrospective analyses of data from the I-Lan Longitudinal Aging Study (ILAS) to develop a prediction model, and from the Longitudinal Aging Study of Taipei (LAST) for external validation. *Setting:* Community-dwelling adults from Taipei City, New Taipei City and Yilan (I-Lan) County, Taiwan. *Participants:* 1271 community residents ≥65 years old, without impaired global cognition or dependency for activities of daily living/instrumental activities of daily living. *Measurements:* Demographic characteristics, anthropometric measurements, medical history, Mini-Mental State Examination, Montreal Cognitive Assessment, Functional Autonomy Measuring System, Functional Assessment Staging Test, Center for Epidemiologic Studies Depression Scale, handgrip strength, 6-metre walk speed. *Methods:* Baseline characteristics of groups with/without cognitive frailty were analyzed and factors differing significantly in univariate analysis input to binary logistic regression to develop a cognitive frailty risk (CFR) score. *Results:* The prevalence of cognitive frailty was 15.8% overall; ILAS 21.4%, LAST 8.4%. Predictors of CFR comprised: age ≥75 years; female sex; waist circumference ≥90 cm (male), ≥80 cm (female); calf circumference <33 cm (male), <32 cm (female); memory deficits; and diabetes mellitus. CFR ≥5/14 had sensitivity of 70%, specificity of 60%, and predictive accuracy of 72%. *Conclusions:* A CFR score based on simple history-taking and anthropometric measurements integrates age, sex, cardiometabolic risk, memory deficits, sarcopenia, and nutrition, with validated predictive accuracy, and could be performed easily in community settings to identify seniors with cognitive frailty for appropriate interventions.

Key words: Cognitive frailty, screen, tool, community, elder, age.

Introduction

Population aging poses great challenges both globally and especially for Taiwan, which is among the fastest aging nations (1). The World Report on Aging and Health defines healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing in older age" (2); its strong emphasis on maintaining functional capacity aims to prevent disability and dementia in later life through a life-course approach.

Dementia and frailty are common age-related chronic conditions that substantially increase healthcare needs and are inimical to quality of life in older people. Although physical frailty and cognitive impairment are often researched separately, previous studies have shown that they are strongly associated and may have overlapping pathogenesis (3). Consequently, reciprocal physical and cognitive decline has been defined as "cognitive frailty", which studies have shown to be associated with poor quality of life, incident dementia, disability and mortality (4-6). Ideally, the operational criteria should include people who are at risk for adverse outcomes that are potentially reversible, to promote healthy aging. Accordingly, two conceptual subtypes of cognitive frailty have been proposed – potentially reversible (7, 8) and reversible (9) as defined by concurrent early declines in physical and cognitive domains (ie, pre-mild cognitive impairment and pre-frailty).

The principal phenotypic components of physical frailty are not all equally associated with adverse outcomes – mobility impairments (slowness and weakness) are stronger predictors than others (10). Besides being critical determinants of physical frailty, slowness and/or weakness are also significantly associated with cognitive impairment (11). On the other hand, pre-mild cognitive impairment is defined as cognitive performance 1.5 standard deviations below age-, sex- and education-adjusted norms on standardized neuropsychological tests (12, 13).

Although the concept of cognitive frailty was postulated to facilitate earlier identification of elders at risk for adverse health outcomes, epidemiological evidence supporting the current operational definitions was lacking, until recently (14-16). The biggest challenge in diagnosing cognitive frailty

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was that most previous studies used comprehensive but time-consuming instruments to assess cognitive function (17). Shimada et al used an organized battery (NCGG-FAT), and demonstrated that cognitive frailty significantly predicted incident dementia among community-dwelling older people.18 Since detecting early cognitive decline remains difficult, developing an effective case-finding protocol is crucially important to identifying people at risk for cognitive frailty who need comprehensive assessment. Hence, the purpose of this study was to develop a simple questionnaire and anthropometric battery for identifying community-dwelling older people at risk of cognitive frailty.

Methods

Study design and population samples

Study data were excerpted from two population-based aging cohort studies in Taiwan, the I-Lan Longitudinal Aging Study (ILAS) and the Longitudinal Aging Study of Taipei (LAST), which both recruited people ≥50 years old; this study excluded ILAS and LAST participants younger than 65 or with impaired global cognition or functional dependency (Figure 1). The criteria defining impaired global cognitive function were: 1) total Mini-Mental State Examination (MMSE) score <24 in ILAS participants educated for ≥6 years, or MMSE <14 in those with >6 years of education;19 2) total Montreal Cognitive Assessment (MoCA) score <26 in LAST participants, with one point added to the total score in those with ≤12 years education.20 Functional dependence was defined as impairment in any domain of activities of daily living or instrumental activity of daily living in either cohort, according to the Functional Autonomy Measuring System (21).

This study was conducted according to the ethical principles established by the Declaration of Helsinki. The Institutional Review Boards have approved the protocol. ILAS and LAST participants provided written informed consent.

Demographic data

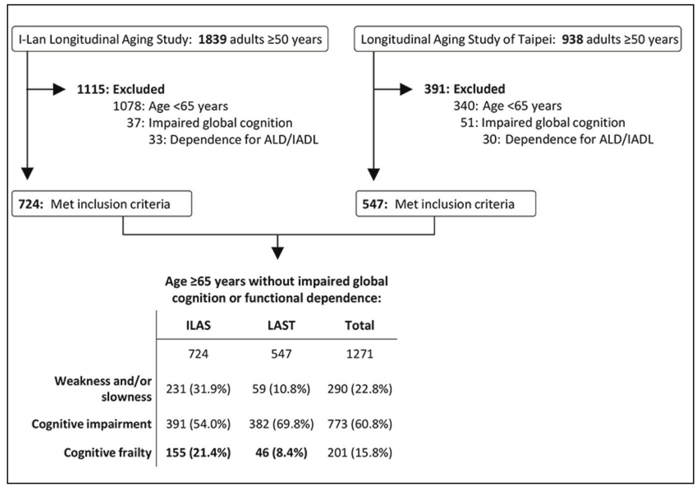
Trained research nurses collected participants demographic information (age, sex, education years) and health-related (tobacco and alcohol use, medical history) and anthropometric data (height, weight, waist circumference, calf circumference), and conducted cognition, mood, and functional assessments including the Functional Assessment Staging Test, Center for Epidemiologic Studies Depression Scale (CES-D), MMSE, MoCA, and Functional Autonomy Measuring System.

Definition of physical declines in cognitive frailty

This study used only slowness and weakness to define physical pre-frailty, based on earlier research;16 slowness was defined as 6-metre walk speed <0.8m/s, and weakness as handgrip strength <26 kg for men and <18 kg for women (22).

Figure 1

Study sample selection and disposition



ADL, activities of daily living; IADL, instrumental activities of daily living; ILAS, I-Lan Longitudinal Aging Study; LAST, Longitudinal Aging Study of Taipei.

Definition of cognitive impairment in cognitive frailty

Cognitive impairment was defined as declines in any cognitive domains that met criteria for cognitive frailty. LAST assessed cognitive function using MoCA, which includes short-term memory, visuospatial ability (clock drawing test, cube copy task), executive functioning (trail making test Part B, phonemic fluency, verbal abstraction), attention, concentration, and working memory (target detection, serial subtraction, digits forward and backward), language (confrontation naming with low-familiarity animals, repetition of complex sentences), and orientation to time and place (23). ILAS used multiple neuropsychological assessments to evaluate four cognitive domains: verbal memory (delay-free recall in the Chinese Version Verbal Learning Test), language function (Boston Naming Test, category (animal) Verbal Fluency Test), visuospatial function (Taylor Complex Figure Test), and executive function (Digit Backward Test, Clock Drawing Test). Participants with scores in any cognitive domain below 1.5 standard deviations of age-, sex-, and education-matched subjects were considered cognitively frail.

Risk prediction model development and validation

ILAS data, including all medical and personal details and anthropometric measurements currently recorded in annual senior health examinations in Taiwan, were used to develop a prediction model. Cut-off thresholds for continuous variables were based on published guidelines: age = 75 years (24); central obesity = waist circumference ≥90 cm for men, ≥80 cm for women (25); calf circumference = 33 cm for men, 32 cm for women (26); CES-D score = 16 points (27). Variables with statistical significance ($p < 0.05$) in univariate analysis were input to binary logistic regression and coefficients of variables with statistical significance ($p \leq 0.25$) in binary logistic regression were converted into integer scores; the summed

Table 1
Characteristics of ILAS participants with versus without cognitive frailty

Data show mean ± standard deviation or number (%)	Total	Cognitively frail	Not cognitively frail	P*
Number	724	155 (21.4%)	569 (78.6%)	
Demographic and anthropometric data				
Age	73.1 ± 5.4	75.4 ± 5.5	72.4 ± 5.2	0.392
Age ≥75 years	259 (36)	85 (55)	174 (31)	<0.001
Sex (female)	339 (47)	97 (63)	242 (43)	<0.001
Body mass index (kg/m2)	24.8 ± 3.5	24.8 ± 4.0	24.8 ± 3.3	0.830
Waist circumference (cm)	86.7 ± 9.5	87.3 ± 10.8	86.6 ± 9.1	0.440
≥90 cm (male), ≥80 cm (female)	404 (56)	100 (65)	304 (53)	0.014
Calf circumference (cm)	32.8 ± 3.0	32.0 ± 3.1	33.0 ± 3.0	0.417
≥33 cm male), ≥32 cm (female)	306 (42)	80 (52)	226 (40)	0.008
Visual acuity ≤0.5 (logMAR)	100 (14)	17 (11)	83 (15)	0.247
Education (years)	3.3 ± 4.3	1.7 ± 3.0	3.7 ± 4.5	<0.001
Health-related risk factors				
Tobacco smoker	233 (32)	41 (26)	192 (34)	0.085
Take alcohol	188 (26)	26 (17)	162 (28)	0.003
Diabetes mellitus	146 (20)	41 (26)	105 (18)	0.028
Hypertension	384 (53)	87 (56)	297 (52)	0.385
Dyslipidemia	57 (8)	13 (8)	44 (8)	0.789
Coronary artery disease	57 (8)	13 (8)	44 (8)	0.789
Subjective symptoms				
Exhaustion	37 (5)	14 (9)	23 (4)	0.012
Weight loss	35 (5)	10 (6)	25 (4)	0.290
Memory complaints	30 (4)	13 (8)	17 (3)	0.003
Depression	24 (3)	15 (10)	9 (2)	<0.001
Functional assessment				
Gait speed (m/s)	1.3 ± 0.4	1.1 ± 0.4	1.4 ± 0.4	0.786
Handgrip strength (kg)	25.3 ± 8.2	17.6 ± 5.1	27.4 ± 7.6	<0.001

ILAS, I-Lan Longitudinal Aging Study; *Significance level P ≤0.05.

integers for each variable constituted the cognitive frailty risk (CFR) score.

Statistical analysis

Continuous variables were compared by Student's t-test and categorical variables with Chi-square tests. Binary logistic regression analysis with backward stepwise variable selection used an entry criterion of p ≤0.25. Discrimination was expressed as area under the receiver-operating curve and the Hosmer-Lemeshow test evaluated goodness of fitness. Internal validation used a bootstrap technique with 1000 resamples from the developmental dataset (ILAS). The CFR scoring system developed was applied to LAST data for external validation, and its effectiveness evaluated based on accuracy and area under the receiver-operating curve. All analyses used SPSS Statistics for Windows, Version 24.0 (IBM Corp. Armonk, NY). A two-tailed p-value <0.05 was considered statistically significant.

Results

Among 1271 ILAS and LAST participants without global cognitive impairment or functional dependence, 773 had cognitive impairment, 290 dynapenia, and 201 cognitive frailty (Figure 1); the prevalence of cognitive frailty in ILAS was 21.4% in ILAS and 8.4% in LAST. Table 1 shows the baseline characteristics of ILAS participants (development cohort) with versus without cognitive frailty; between-group differences

Table 2
Risk factors for cognitive frailty in logistic regression analysis, and their weighted scores

Predictive factors*	Odds ratio (95% CI)†	β-coefficient	Cognitive Frailty Risk score points
Age ≥75 years	2.56 (1.73–3.79)	0.94	3
Female sex	2.07 (1.36–3.16)	0.76	3
Waist circumference ≥90 cm (male), ≥80 cm (female)	1.40 (0.91–2.16)	0.34	1
Calf circumference <33 cm (male), <32 cm (female)	1.77 (1.17–2.65)	0.57	2
Memory deficits	2.83 (1.28–6.24)	1.04	4
Diabetes mellitus	1.30 (0.83–2.04)	0.25	1
Cognitive Frailty Risk score (maximum)			14

CI, Confidence interval; *Significance level p ≤0.25; †Adjusted for years of education.

Table 3
Cognitive Frailty Risk score sensitivity, specificity and odds ratios at different cut-offs

CFR cut-off	≥4	≥5	≥6	≥7	≥8
Sensitivity	81%	70%	53%	39%	29%
Specificity	42%	60%	79%	87%	93%
Odds ratio (95% CI)	3.17 (2.05–4.91)	3.62 (2.47–5.32)	4.16 (2.86–6.05)	4.10 (2.74–6.13)	5.27 (3.29–8.43)

CFR, Cognitive Frailty Risk score; CI, confidence interval.

in age, female sex, central obesity, low calf circumference, education years, alcohol consumption, diabetes mellitus, and subjective symptoms of exhaustion, depressive symptoms, memory complaints, and handgrip strength were statistically significant and these variables were used for further model development.

Binary logistic regression analysis identified six independent factors associated with cognitive frailty: age ≥75 years, female sex, central obesity, low calf circumference, memory complaints, and diabetes mellitus. Table 2 shows the results of multivariate analysis and the corresponding scores assigned to predict cognitive frailty; the minimum CFR score was zero and the maximum 14. The derived model had good fitness (Hosmer-Lemeshow test, p = 0.48) and discrimination with a bootstrap-corrected C-statistic of 0.71 when the cut-off was defined as CFR ≥5 (Figure 2). The highest accuracy was 79% at CFR ≥8.

Table 3 shows the sensitivity, specificity, and CFR odds ratios of the prediction model at different cut-offs; the highest sensitivity was 81% at CFR ≥4, and the highest specificity was 93% at CFR ≥8. CFR sensitivity and specificity scores were compared to determine the final cut-off of ≥5. Figure 2 summarizes comparisons between the development and validation cohorts, the validation cohort had somewhat better overall accuracy than the developmental cohort, with a C-statistic of 0.69 and accuracy of 72%.

Discussion

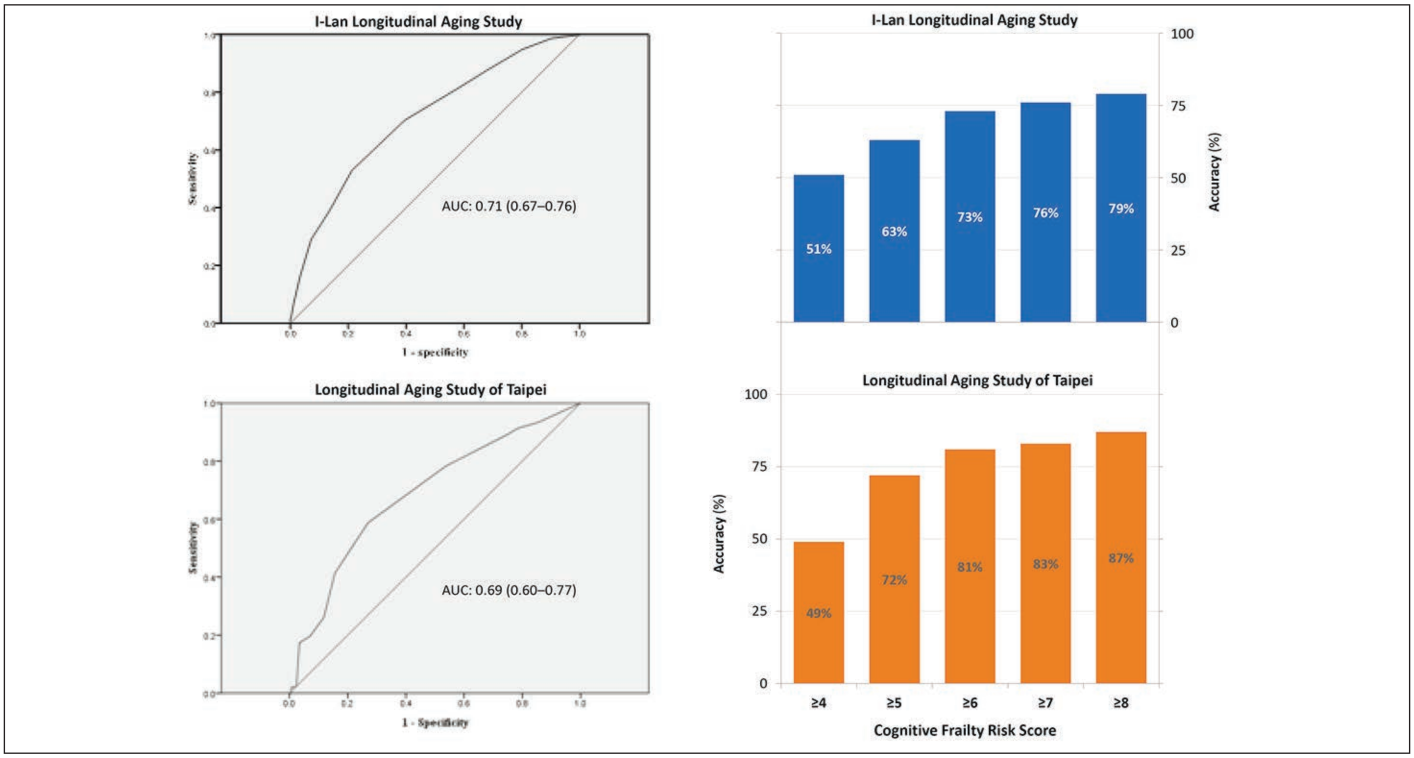
We have innovated and validated an algorithm to screen for cognitive frailty in older people based on simple history-taking and anthropometric measurements, which would be easy to implement in community settings to identify seniors in need of appropriate intervention.

The overall prevalence of cognitive frailty in this study was 15.8%, higher than in others that used The International Association for Gerontology and Geriatrics/International Academy of Nutrition and Aging definition (1.0% to 4.4%).28 Higher prevalence in ILAS than in LAST (21.4% vs 8.4%) may reflect different of education levels between these cohorts; however, cognitively frail people in either cohort had similar demographic profiles; specifically older age, less educated, and female predominance. Cognitive frailty as defined in this study may predict all-cause mortality and dementia (16, 29) which provides strong epidemiological support for this operational definition.

Despite its clinical significance, identifying cognitive frailty in community settings is arduous, due to the need for extensive neuropsychological examinations. Therefore, a pragmatic screening algorithm for cognitive frailty is an important step towards developing targeted interventions. Our CFR score has satisfactory sensitivity, specificity and predictive accuracy; CRF ≥5 (sensitivity 70%, specificity of 60%, prediction accuracy 72%) is considered positive, but needs further

Figure 2

Accuracy and discrimination (AUC) of Cognitive Frailty Risk score in predicting cognitive frailty in the development (ILAS) and validation (LAST) cohorts



AUC, area under receiver-operating characteristic curve; ILAS, I-Lan Longitudinal Aging Study; LAST, Longitudinal Aging Study of Taipei. Diagonal line indicates an ideal calibration curve.

confirmation.

The etiology of cognitive frailty involves vascular, nutritional, psychosocial, and metabolic risk factors, and sarcopenia;29 the development of physical frailty is also multifactorial, with females disproportionately affected,30,31 and similar characteristics are associated with susceptibility to dementia. Calf circumference is an established surrogate for lean body mass and nutritional status (26, 32) so this component of CFR may represent the contributions of sarcopenia and physical frailty to cognitive frailty. Although Korean researchers have suggested using calf circumference as a cognitive frailty screening tool (33) a composite score may prove more informative. Central obesity is closely associated with cardiovascular risk (34), and diabetes mellitus is independently associated with cognitive frailty (28); these comorbidities may therefore connote cardiometabolic risk. Subjective memory deficit is an early indicator of cognitive impairment and is a criterion for diagnosing reversible cognitive frailty (9). Hence, this innovatory CFR score covers age, sex, cardiometabolic risk, memory, sarcopenia and nutrition, with satisfactory predictive accuracy.

This study had some limitations. First, the development (ILAS) and validation (LAST) cohorts had different demographic characteristics and consequently, different epidemiology of cognitive frailty. Nevertheless, congruent results support using the CFR score to screen for cognitive frailty in different communities. Second, mood was evaluated by CES-D and the average score was far below the cut-off value for depression, which may limit the utility of CFR among people with more depressive symptoms. Third, cultural differences may limit generalizability to older people in different socio-cultural contexts.

Conclusions and implications

We have developed a pragmatic, evidence-based cognitive frailty screening tool, based on simple health-related metrics that are easily ascertained in everyday practice, which integrates diverse known risk factors. The CFR scoring system has validated predictive accuracy and may facilitate the identification of seniors with cognitive frailty for appropriate targeted intervention. The individual risk factors associated with cognitive frailty may also shed light on its underlying pathoetiology.

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Ethical standard: The institutional review board of Taipei Veterans General Hospital and National Yang Ming University have approved the whole study.

Conflict of interest: All authors declare no conflict of interest.

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