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Original Study

Frailty in Older Persons: Multisystem Risk Factors and the Frailty Risk Index (FRI)

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A B S T R A C T

Importance: Currently there is no risk factor scale that identifies older persons at risk of frailty.
Objectives: In this study, we identified significant multisystem risk factors of frailty, developed a simple frailty risk index, and evaluated it for use in primary care on an external validation cohort of community-living older persons.
Design, Setting, and Participants: We used cross-sectional data of 1685 older adults aged 55 and older in the Singapore Longitudinal Ageing Studies (SLAS) to identify 13 salient risk factors among 40 known and putative risk factors of the frailty phenotype (weakness, slowness, low physical activity, weight loss, and exhaustion). In a validation cohort (n = 2478) followed for 2 years, we evaluated the validity of Frailty Risk Index (FRI).
Main Outcomes and Measures: Frailty at baseline and functional dependency, hospitalization, and SF12 physical component summary (PCS) scores at 2-year follow-up were measured among people in the validation cohort.
Results: The components (weighted scores) of the FRI are age older than 75 (2), no education (1), heart failure (1), respiratory disorders (2), stroke (2), depressive symptoms (3), hearing impairment (3), visual impairment (1), FEV_1/FVC lower than 0.7 (1), eGFR lower than 60 mL/min/1.73m^2 (1), nutritional risk score of 3 or higher (2), anemia (1), and white cell counts ($\times 10^9$/L) of 6.5 or more (1). In the validation cohort, the FRI (0 to 12) was significantly associated with prefrailty (OR, 1.20 per unit; 95% CI 1.19–1.27) and frailty (OR 1.80 per unit; 95% CI 1.65–1.95). The FRI predicted subsequent IADL-ADL dependency (OR1.19; 95% CI 1.11–1.27), hospitalization (OR .14; 95% CI 1.05–1.24), lowest quintile of SF12-PCS (OR 1.17; 95% CI 1.11–1.25), and combined adverse health outcomes (OR 1.16; 95% CI 1.09–1.22).
Conclusions and Relevance: The FRI is a validated instrument for assessing frailty risk in community-living older persons. FRI may be a useful rapid assessment tool to identify vital body system deficits underlying the frailty syndrome.

Frailty is a commonly recognized geriatric syndrome in clinical practice. Frail elderly persons are vulnerable to increased risk of dependency in activities of daily living, hospitalization, institutionalization, and dying when exposed to stress. There is current consensus that physical frailty is potentially reversible. It is hence useful to objectively detect frailty among frail elderly persons, as frailty indices serve a useful purpose for risk stratification, predicting need for institutional care and planning of services needed.[1]

The Cardiovascular Health Study (CHS) frailty scale, consisting of a combination of syndrome components (weight loss, exhaustion, weakness, slowness, and reduced physical activity),[2] is the most widely used measure of frailty in research, but is cumbersome for routine use in clinical settings.[3] It defines frailty distinctly as a clinical syndrome, and does not include risk factors. So far, no scale has been developed to identify older persons at risk of frailty based on their profile of important risk factors. Other frailty scales, based on the

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cumulative deficit model or the multidimensional model, such as the Frailty Index,[4] Frailty Index Comprehensive Geriatric Assessment (FI-CGA),[5] the Multidimensional Prognostic Index (MPI) Index,[6] the FRAIL,[7] and Gérontopôle Frailty Scale (GFS),[8] include psychosocial, medical risk factors, and ADL disability, but conflate risk factors with adverse outcomes.

As frailty is a biologic syndrome due to multisystem declines in physiological reserves, a large number of direct, indirect, and interacting risk factors are involved in its causation.[9] They include low socioeconomic status, living alone, comorbidity, specific chronic diseases, heart failure, anemia, diabetes, depression, cognitive impairment, poor nutrition such as micronutrient deficiency, obesity, low cholesterol, and immune markers of chronic inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6).[10–26] Few studies have simultaneously investigated diverse and overlapping risk factors together in the same participants to identify a minimal subset of unique multisystem clinical indicators of frailty risk. In this study, we developed a frailty risk prediction tool based on simple and routine clinical measurements and externally validated it for use in primary care using data from 2 cohorts of community-living older persons.

Method

Population Samples

The development and validation studies were conducted in 2 separate cohorts in the Singapore Longitudinal Ageing Studies. The first-wave cohort (SLAS-1, n = 2805) recruited residents in the southeast region of Singapore between 2003 and 2004, and followed them up at 2 years and 4 years. A second-wave cohort (SLAS-2) used identical methodologies and completed baseline survey for residents in the southwest and south central regions of Singapore from 2010 to 2013 (n = 2010 as of April 30, 2013). Previous publications have detailed the SLAS study design, population sampling, and measurements.[27] The research was approved by the National University of Singapore Institutional Review Board, and informed consent was obtained from all participants (response rate 78%). At baseline, all participants underwent 5 to 6 detailed interview sessions in their homes, and on-site clinical assessments, performance-based testing, and venesection by trained research personnel for an extensive range of demographic, medical, biological, psychosocial, behavioral, and neurocognitive variables.

The development study was conducted in the SLAS-2 sample, and investigated 40 known and putative risk factors of phenotypic frailty, excluding correlates such as difficulties in activities of daily living (ADLs) and history of hospitalization, which are congruent outcomes of frailty. We identified 14 independent multisystem risk factors among them and derived a Frailty Risk Index (FRI). The FRI was externally validated in the SLAS-1 cohort on its ability to predict the prevalence of frailty at baseline and subsequent likelihood of functional dependency, hospitalization, and impaired quality of life at 2-year follow-up.

The development study was based on baseline data of 1685 participants, after excluding participants for whom data were not available at the time for white cell counts (n = 328) and/or lymphocyte counts (n = 271). The validation study was conducted on 2478 participants in the SLAS-1 with complete baseline data, and on 1585 participants who had complete follow-up data on instrumental ADL (IADL)-ADL dependency, hospitalization, and Short Form 12 Physical Component Summary (SF12-PCS) measure of quality of life.

Measurements

In the development cohort, the physical frailty phenotype was defined using 5 criteria proposed and validated in the Cardiovascular Health Study (CHS)[2]: unintentional shrinking, slowness, weakness, exhaustion, and low activity. The measurements used in this study to define the frailty construct were similar but not identical to those used in the original CHS study. A participant without any of the 5 components was defined as nonfrail, 1 to 2 components as prefrail, and 3 and more components as frail.

1. Unintentional shrinking: body mass index (BMI) of less than 18.5 kg/m^2 and/or unintentional weight loss of 10 pounds (4.5 kg) or more in the past 6 months.
2. Slowness was assessed using the 6-meter fast gait speed test, using the average of 2 measurements, and the lowest quintile values stratified for gender and height to classify participants as slow.
3. Weakness: leg muscle strength was determined using dominant knee extension, using the average value from 3 trials in kilograms, standardized on gender and BMI strata. Participants with knee extension strengths in the lowest quintiles were classified as weak.
4. Exhaustion was measured with 3 questions on vitality domain in the Medical Outcomes Study SF-12[28]: "Did you feel worn out?" "Did you feel tired?" "Did you have a lot of energy?" with total summed scores ranging from 3 to 15, and a higher score indicating more energy. A score of less than 10 was used to denote exhaustion.
5. Low activity: physical activities were assessed based on self-reported time (in hours) spent doing light (eg, office work, driving a car, strolling, standing with little motion, personal care), moderate, and vigorous activities (eg, gardening, brisk walking, dancing, jogging, swimming, strenuous sports) on weekdays and the weekend. The total amount of time spent on performing moderate and vigorous activities per week and activity time below the gender-specific lowest quintile was used to denote frailty on this criterion.

In the validation cohort, the CHS criteria for phenotypic frailty were modified based on the available data. Weakness was defined by the lowest quintile of performance on rising from chair test; slowness was defined by Performance-Oriented Mobility Assessment gait performance score of 8 or lower; exhaustion was defined by their response ("not at all") to "Did you have a lot of energy?"; low activity was defined by "none" self-report of participation in any physical activity (walking or recreational or sports activity).

Another frailty scale, the FRAIL scale,[7] is a simple rapid screening test that has been developed and validated to allow physicians to identify persons with the physical frailty syndrome for more in-depth assessment. Accordingly we used data of the SLAS-1 participants to score their responses (0 or 1) to Fatigue: energy (none of the time); Resistance: climb stairs (limited a lot), Aerobic: activity or work (limited a lot); Illnesses: 5 or more illnesses; Loss of weight: unintended loss of 10 lb/4 kg in past 6 months, and classified them as follows: frail, 3 or more; prefrail: 1 or 2. The FRAIL scale was used in addition to the CHS Frailty scale as comparators in evaluating the ability of the FRI scale to predict adverse health outcomes.

Candidate Variables

The candidate variables selected as potential predictors of the FRI are well established or putative risk factors for physical frailty, and were not congruent characteristics of frailty. Difficulties in performing IADL-ADL activities, history of hospitalization, falls, and symptoms congruent with physical frailty (such as climbing stairs, physical work limitations, breathlessness) were excluded. Available biomarkers of nutrition and inflammation, such as CRP, IL-6, folate, B12,

homocysteine, and others, were not used because they are not routinely used in primary care settings, but biomarkers such as low hemoglobin, white cell counts (WCCs), and lymphocyte counts were used instead. Low hemoglobin is reportedly associated with frailty and with elevated levels of circulating IL-6 levels in frail older adults. WCC is a recognized cellular marker of systemic inflammation and reportedly associated with frailty.[15,20]

Sociodemographic data included age, gender, ethnicity, education, housing type (an indicator of socioeconomic status), marital status, and living arrangement. *Life style variables* included self-reports of current smoking and daily alcohol drinking. The self-report of a medical disorder diagnosed and treated by a physician(s) was recorded for 22 named diagnoses and other disorders. The presence of hypertension, dyslipidemia, diabetes, and cardiac diseases was supported by examination of medications used, physical examination or blood tests, electrocardiogram, fasting blood glucose, or history of coronary reperfusion procedures. The number of *comorbidities* was estimated from the total count of medical disorders in the past 1 year. *Medications* (prescription and over-the-counter) used by the participant in the past year were ascertained from self- or proxy-reports and physical inspection of labels on pill bottles, boxes, and packets. Polypharmacy was defined as the use of 6 or more medications. *Depressive symptoms* was measured by the Geriatric Depression Scale (GDS), which has been validated for use in local Chinese, Malay, and Indian participants.[29,30] Scores range from 0 to 15, with a higher score indicating more symptoms of depression, and a score of 5 or higher denoting a clinically significant level of depressive symptoms. *Cognitive function* was evaluated by using translated and modified versions of the Mini-mental State Examination (MMSE) that have been validated for local use in Singaporean older adults.[31] A score of 23 or less denoted cognitive impairment. *Orthostatic hypotension* was determined by a systolic blood pressure (BP) drop of at least 20 mm Hg (irrespective of the diastolic change), a diastolic BP drop of at least 10 mm Hg (irrespective of the systolic change), or a drop in either (consensus OH) 3 minutes after standing up from a supine position.[32] *BMI* in kg/m^2 was analyzed as a binary variable (obesity versus no obesity) using 30 kg/m^2 as a cut point. *Nutrition risk score* was assessed by a 10-item questionnaire recommended in the Nutrition Screening Initiative (DETERMINE Your Nutritional Health).[33,34] The summed weighted scores range from 0 to 21, with a higher score indicating poor nutritional status; a score of 3 or higher was used to categorize a participant having high-risk nutritional status. *Blood tests* include hemoglobin (g/dL), albumin (g/dL), lymphocytes ($\times 10^9$/L), WCCs ($\times 10^9$/L), and total cholesterol (mmol/L). Fasting venous blood was collected from each respondent after an overnight fast of 10 hours. Anemia was defined using World Health Organization criteria: hemoglobin lower than 12 g/L in women and lower than 13 g/L in men. Low albumin was defined as values lower than 40 g/L. High cholesterol was defined as values of 6.5 mmol/L or higher. Low WCCs and lymphocyte counts were defined by values in the corresponding lowest tertiles. *Pulmonary function* was assessed by the ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC). Values of FEV_1/FVC below 0.7 indicate chronic airflow obstruction. Visual impairment was defined as having corrected binocular vision worse than 20/40, as used in other studies.[35] *Hearing impairment* was assessed using self-report and the standard whisper test.

Functional dependency was assessed by self-reported difficulty and requiring help on 1 or more IADL or basic ADL activities, previously validated for use in the local population.[36,37] *Hospitalization* was determined by the participants' self-reports of new hospitalizations for any chronic medical conditions over the previous year. Quality of life was measured using the Medical Outcomes Study SF12-PCS of quality of life.[28]

Data Analysis

All social-demographic, health, biochemical, and other characteristics of the participants were dichotomized and described using proportions. Bivariate associations of potential risk indicator variables with frailty defined by the CHS Frailty scale were analyzed based on the Cochran-Mantel-Haenszel test. ADL disability, IADL disability, falls, and hospitalization were not included as candidate risk predictor variables in the selection models. Stepwise logistic regression ($P < .05$ for entry and $P < .05$ for retention in the model) was performed to select significant independent predictors of frailty. All variables were entered as candidate predictor variables in the initial regression model. The strengths of associations were estimated by odds ratio (OR) and 95% confidence interval (CI).

A summary risk score for frailty was derived from the β coefficients associated with the significant predictor variables in the final selection model for frailty. We assigned a risk score for each variable based on its coefficient value, standardized with the lowest value, which was assigned a value of 1, and rounded to the nearest integer. The summary risk score for an individual was obtained by summing the weighted scores of each of the risk factors.

Validation of the FRI on the external validation sample was performed by analyzing the association of the FRI score as a continuous variable with the observed proportions of prefrailty and frailty in multinomial logistic regression models, and estimating the OR (95% CI) of prefrailty and frailty associated with each unit of FRI score in the baseline sample, together with receiver operating characteristics (ROC) analyses. In the prospective follow-up data, longitudinal associations of the FRI with adverse health outcomes (IADL-ADL disability, hospitalization, lowest quintile of SF12-PCS) at the 2-year follow-up were analyzed. The ability of the FRI to predict adverse health outcomes was compared with the CHS Frailty scale and the FRAIL scale. The relationships were analyzed on the whole sample (n = 1585) and on a sample of participants who were free of adverse health outcome at baseline.

A 2-sided *P* value of less than .05 was considered as statistically significant. All analyses were performed by SAS (SAS Institute, Inc, Cary, NC).

Results

In the development cohort (mean age, 66.7; SD, 7.76), 5% (n = 90) were frail and 42% (n = 712) were prefrail. All but a few of the candidate predictor variables were significantly associated with prefrailty-frailty (Table 1). All variables (except ADL disability, IADL disability, hospitalization, and falls) were entered in a stepwise backward selection prediction model of frailty (Table 2). A total of 13 significant variables were derived in the final selection model. They were older age, having no education, heart failure, obstructive respiratory disorders (asthma and/or chronic obstructive pulmonary disease [COPD]), stroke, depressive symptoms, hearing impairment, visual impairment, chronic airflow obstruction (FEV_1/FVC<0.70), chronic kidney failure (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), low hemoglobin, high nutritional risk, and increased WCCs. Table 2 shows the β coefficients and ORs for prefrailty-frailty derived from this model and the risk scores assigned to each risk factor.

Risk scores assigned to each of these risk factors were summated, and in the validation cohort, the summary risk score (FRI) was related to the prevalence of prefrailty and frailty (Table 3). Increasing summed scores of FRI were clearly related to increasing prevalence of prefrailty and frailty (Figure 1). In multinomial regression models analyzing FRI as a continuous variable, the risk of frailty increased by an estimated 80% per unit of FRI score, and 23% per unit of FRI score

Table 1
Bivariate Association of Measured Variables With Frailty in Development Cohort (n = 1685)

Factor	Robust n = 883	Prefrail n = 712	Frail n = 90	*P* Value
Age 75+	70 (7.9)	144 (20.2)	33 (36.7)	<.001
Female	566 (64.1)	457 (64.2)	61 (67.8)	.66
No formal education	133 (15.1)	186 (26.1)	31 (34.4)	<.001
Low-end (1–2 room) public housing	147 (16.7)	182 (25.6)	37 (41.1)	<.001
Non-Chinese ethnicity	79 (9.0)	90 (12.6)	13 (14.4)	.010
Single, divorced, widowed	256 (29.0)	280 (39.3)	47 (52.2)	<.001
Living alone	114 (12.9)	133 (18.7)	24 (26.7)	<.001
Current smoking	173 (19.7)	181 (25.5)	24 (27.3)	.004
Daily alcohol drinking	30 (3.4)	17 (2.4)	1 (1.1)	.114
No. of chronic medical problems (>5)	157 (17.8)	195 (27.4)	47 (52.2)	<.001
Cardiovascular disease	50 (5.7)	75 (10.5)	14 (15.6)	<.001
Hypertension	513 (58.1)	454 (63.8)	72 (80.0)	<.001
Diabetes	151 (17.1)	170 (23.9)	28 (31.1)	<.001
Stroke	14 (1.6)	29 (4.1)	11 (12.2)	<.001
Coronary heart disease	28 (3.2)	32 (4.5)	7 (7.8)	.028
Atrial fibrillation	19 (2.2)	31 (4.4)	4 (4.4)	.016
Heart failure	6 (0.7)	16 (2.3)	3 (3.3)	.003
Cataracts/glaucoma	232 (26.3)	234 (32.9)	46 (51.1)	<.001
Asthma/COPD	28 (3.2)	44 (6.2)	10 (11.1)	<.001
Thyroid disease	41 (4.6)	41 (5.8)	1 (1.1)	.86
Arthritis	119 (13.5)	112 (15.7)	18 (20.0)	.063
Osteoporosis	41 (4.6)	48 (6.7)	11 (12.2)	.003
Gastrointestinal problems	52 (5.9)	56 (7.9)	14 (15.6)	.002
Cancer	23 (2.6)	16 (2.3)	6 (6.7)	.29
Chronic kidney disease	40 (4.5)	77 (10.8)	17 (18.9)	<.001
Poor self-rated health	3 (0.3)	9 (1.3)	6 (6.7)	<.001
Depressive symptoms (GDS ≥5)	7 (0.8)	20 (2.8)	9 (10.0)	<.001
Cognitive impairment (MMSE score ≤23)	36 (4.1)	60 (8.4)	20 (22.2)	<.001
Polypharmacy (>5 drugs)	88 (10.0)	143 (20.1)	26 (28.9)	<.001
Orthostatic hypotension	9 (1.0)	18 (2.5)	1 (1.1)	.098
Obesity (BMI ≥30)	45 (5.1)	53 (7.4)	12 (13.3)	.002
High nutritional risk (score ≥3)	193 (21.9)	267 (37.5)	48 (53.3)	<.001
Low albumin (<40 g/L)	78 (8.8)	94 (13.2)	17 (18.9)	<.001
Anemia	308 (34.9)	292 (41.0)	43 (47.8)	.002
Low total cholesterol (0~5.19 mmol/L)	411 (47.0)	369 (52.3)	49 (55.1)	.022
Low lymphocyte counts (0~2.14 x 10^9/L)	586 (67.8)	479 (69.2)	57 (64.8)	.93
WCC ≥6.50 x 10^9/L	244 (27.6)	269 (37.8)	39 (44.3)	<.001
FEV1/FVC <0.7	137 (15.5)	155 (21.8)	28 (31.1)	<.001
Visual impairment	183 (20.7)	226 (31.7)	41 (45.6)	<.001
Hearing impairment	15 (1.7)	29 (4.1)	3 (3.3)	.012
IADL disability	44 (5.0)	78 (11.0)	24 (26.7)	<.001
ADL Disability	2 (0.2)	23 (3.2)	7 (7.8)	<.001
Hospital admission(s)	40 (4.5)	42 (5.9)	9 (10.0)	.033

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GDS, Geriatric Depression Scale; IADL, instrumental ADL; MMSE, Mini-Mental State Examination; WCC, white cell count.
Values are n (%).

(Table 4). The ability of the FRI to predict frailty (CHS Frailty score ≥3) is shown in the ROC curve (Figure 2), with area under the ROC of 0.890.

In longitudinal analyses, FRI scores at baseline were significantly associated with IADL-ADL dependency, hospitalization, lowest quintile of SF12-PCS scores, and combined adverse health outcomes at follow-up, controlling for age, gender, housing status, smoking, multicomorbidity, and baseline IADL-ADL dependency status (or hospitalization in past year, SF12-PCS as appropriate) (Table 5). This was also observed in the sample that excluded participants who had the adverse health outcomes at baseline. The area under the ROC curve for FRI prediction of IADL-ADL dependency was 0.715, relatively greater than the areas under the curve (AUCs) for the CHS Frailty scale and a comparable FRAIL scale (Table 6; Figure 3). Similarly greater AUC values for FRI versus CHS Frailty scale and FRAIL scale were observed for hospitalization and SF12-PCS outcomes.

Table 2
Final Model of Significant Correlates of Prefrailty-Frailty From Binary Logistic Regression Via Backward Stepwise Variable Selection in Development Cohort (n = 1685)

	B	OR	95% CI	*P*	Risk Score
Age ≥75	0.814	2.26	(1.62–3.15)	.000	2
No formal education	0.323	1.38	(1.05–1.81)	.020	1
Heart failure	0.467	1.59	(1.07–2.38)	.022	1
Asthma/COPD	0.532	1.70	(1.02–2.84)	.042	2
Stroke	0.760	2.14	(1.11–4.11)	.023	2
Depression	1.090	2.97	(1.16–7.62)	.023	3
Hearing impairment	0.848	2.34	(1.21–4.52)	.012	3
Visual impairment	0.422	1.52	(1.19–1.95)	.001	1
Low hemoglobin	0.341	1.41	(1.13–1.75)	.002	1
Nutritional risk score ≥3	0.650	1.92	(1.52–2.42)	.000	2
WBC (x 10^9/L) ≥6.5	0.421	1.52	(1.21–1.91)	.000	1
FEV1/FVC <0.7	0.307	1.36	(1.04–1.78)	.026	1
eGFR <60 (mL/min/1.73m^2)	0.449	1.57	(1.01–2.43)	.044	1

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; WBC, white blood cells.
Significant predictors were retained at $P < .05$ in the final model.

Discussion

The exploration of determinants of frailty are important for identifying modifiable risk factors, profiling clinical risk indicators,

Table 3
Clinical Frailty Risk Indicator (C-FRI) Profile at Baseline, Validation Cohort (n = 2478)

Variables	Risk Score	n	%
Whole sample		2478	100
Age ≥75	3	319	12.9
No formal education	2	468	18.8
Heart failure	1	87	3.5
Respiratory problems (asthma, COPD)	2	99	4.0
FEV1/FVC <0.7	1	644	26.0
eGFR<60 (ml/min/1.73m^2)	2	1035	41.8
Stroke	4	92	3.7
Depressive symptoms	4	335	13.5
Hearing impairment	4	67	2.7
Visual impairment	2	837	33.8
Low hemoglobin	1	339	13.7
Nutritional risk score ≥3	3	1229	49.6
WBC (x 10^9/L) ≥6.5	2	715	28.9
Frailty Risk Index (summed scores)			
0		268	10.8
1		357	14.4
2		412	16.6
3		361	14.6
4		281	11.3
5		246	9.9
6		184	7.4
7		145	5.9
8		96	3.9
9		50	2.0
10		30	1.2
11–14		48	1.9
CHS frailty status			
Robust (0)		1290	52.1
Prefrail (1–2)		1105	44.6
Frail (3–5)		83	3.3
FRAIL status			
Robust (0)		1878	75.8
Prefrail (1–2)		580	23.4
Frail (3–5)		20	0.8

CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; WBC, white blood cells.

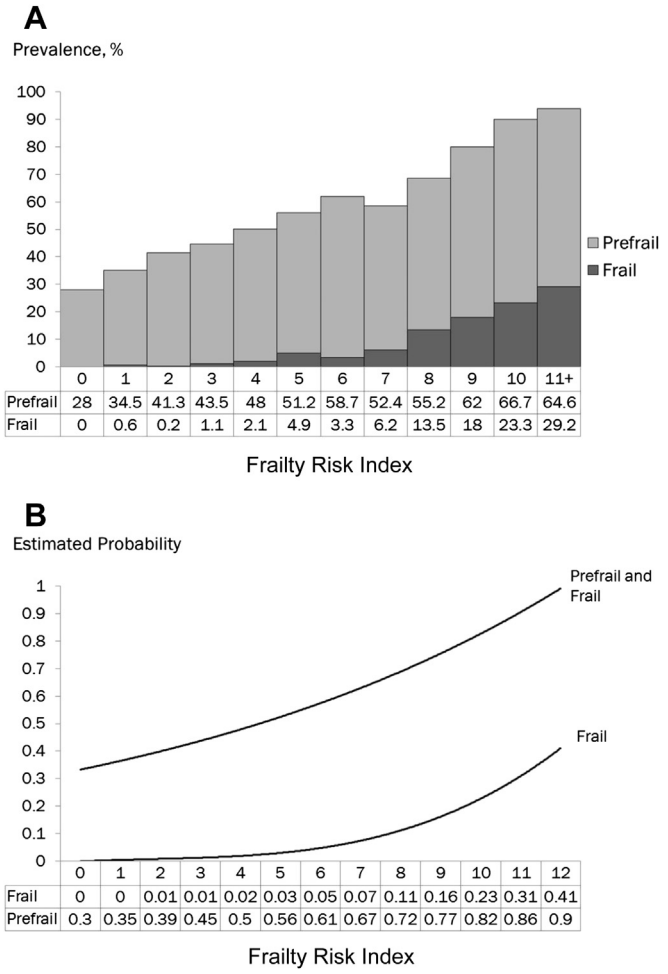

Fig. 1. (A) Prevalence of prefrail and frailty by Frailty Risk Index. (B) Estimated probability of frailty by Frailty Risk Index.

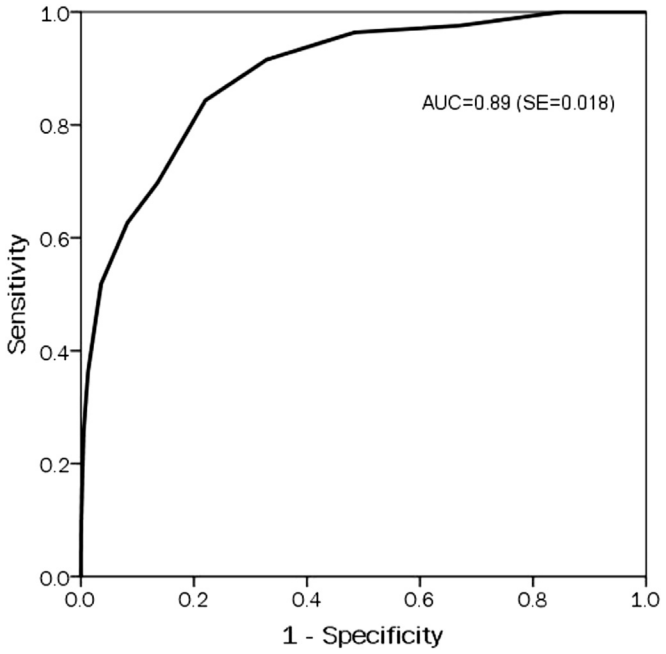

Fig. 2. Receiver operating curve: FRI prediction of frailty (CHS Frailty Index ≥3).

and targeting population subgroups for early intervention among people identified to be at risk of becoming frail. In this study, we investigated 40 known and putative risk factors of frailty, more than any prior studies. The Women's Health Initiative Observational Study (WHI-OS)[38] examined as many as 23 variables, but did not investigate cognitive, nutritional, or blood measurement variables. In this study, all factors, with only 5 exceptions, were found to be associated with frailty in bivariate analyses, consistent with those reported in the WHI-OS. Other studies also have reported positive associations of frailty with age, stroke, COPD/asthma, visual impairment, and anemia.[2,18,19,39–41] Interestingly, both this study and the WHI-OS found that cancer was not associated with frailty.

Depression in particular appeared to be an important contributor, in agreement with other studies.[16–18,42,43] On the other hand, the association of cognitive impairment with frailty, as reported in other studies,[12,44,45] was observed only in bivariate analyses, but failed to be selected in the final model, plausibly because it was substituted by depression, stroke, and congestive heart failure, with which it also shares common pathophysiologic factors, such as atherosclerosis and chronic inflammation.[46,47]

Inadequate dietary intake and nutritional deficiencies are considered important causes of age-related sarcopenia, dynapenia, and frailty.[48,49] Studies have shown that obesity, increased number of micronutrient deficiencies and low serum beta-carotenoids were significant risk factors for frailty,[13,22] although one study using a detailed dietary questionnaire failed to demonstrate that low energy intake was significantly associated with frailty.[49] Our study shows that in place of these nutritional variables, a simple screening measure of poor nutritional risk was independently associated with frailty.

Elevated levels of immune markers of chronic inflammation, such as CRP and IL-6, have been shown to be associated with frailty. In

Table 4
Odds Ratio of Association of Frailty Risk Index With Prefrail and Frail Status: Baseline Analysis, Validation Cohort (n = 2478)

Frailty Risk Index	Prefrail (CHS: 1–2)			Frail (CHS: 3+)		
	OR	95% CI	*P*	OR	95% CI	*P*
Per unit score	1.23	(1.19–1.27)	<.001	1.80	(1.65–1.95)	<.001
0–3	1			1		
4–6	1.9	(1.6–2.3)	<.001	9.3	(3.9–21.9)	<.001
7–9	2.6	(2.0–3.5)	<.001	38.3	(16.4–89.4)	<.001
10–12	14.0	(5.9–32.9)	<.001	433.0	(133.9–1399.6)	<.001

CHS, Cardiovascular Health Study; CI, confidence interval.

Table 5
Association of Frailty Risk Index With Adverse Health Outcomes at 2-Year Follow-up: Validation Cohort, Whole Sample and Baseline AHO-Free Sample (Participants Free of AHO at Baseline)

AHO	Per Unit of Clinical Frailty Risk Score			
	Whole sample		AHO-Free at Baseline	
	OR (95% CI)	*P*	OR (95% CI)	*P*
IADL-ADL dependency	1.19 (1.11–1.27)	<.001	1.16 (1.06–1.26)	<.001
Hospitalization	1.14 (1.05–1.24)	.002	1.17 (1.07–1.28)	<.001
Lowest quintile SF12-PCS	1.17 (1.11–1.25)	<.001	1.22 (1.13–1.33)	<.001
Combined Adverse Health Outcomes	1.16 (1.09–1.22)	<.001	1.20 (1.11–1.30)	<.001

ADL, activities of daily living; AHO, adverse health outcome; CI, confidence interval; IADL, instrumental ADL; SF12-PCS, Short Form 12 Physical Component Summary.
Frailty Risk Index (FRI) was analyzed as a continuous variable in the regression model.
Covariates in model: age, gender, housing status, smoking, multicomorbidity, and baseline IADL-ADL dependency status (or hospitalization in past year/SF12-PCS/SF12-MCS as appropriate).

Table 6
Receiver Operating Characteristic Analyses of FRI, CHS Frailty Scale, and FRAIL Scale Predicting IADL-ADL Dependency, Hospitalization, and Lowest Quintile SF12-PCS Quality of Life, and Any AHO

	IADL-ADL Dependency			Hospitalization			Lowest Quintile SF12-PCS			Any AHO		
	AUC	SE	*P*	AUC	SE	*P*	AUC	SE	*P*	AUC	SE	*P*
FRI Index	0.715	0.018	.0001	0.626	0.027	.0001	0.703	0.015	.0001	0.692	0.014	.0001
CHS Frailty Scale	0.682	0.019	.0001	0.559	0.027	.028	0.637	0.017	.0001	0.634	0.015	.0001
FRAIL Scale	0.624	0.020	.0001	0.598	0.028	.0001	0.618	0.018	.0001	0.613	0.016	.0001

ADL, activities of daily living; AHO, adverse health outcome; AUC, area under the curve; CHS, Cardiovascular Health Study; CI, confidence interval; FRI, Frailty Risk Index; IADL, instrumental ADL; SF12-PCS, Short Form 12 Physical Component Summary.
P indicates significance test of null hypothesis: AUC = 0.50.

turn, circulating IL-6 level is inversely associated with hemoglobin concentration in frail older adults, and low hemoglobin has been found to be independently associated with frailty. WCC is a well-recognized cellular marker of systemic inflammation and found in 2 studies to be associated with greater risk for cardiovascular disease, mortality, and frailty.[15,20] Our study replicates the significant independent association of increased WCC with frailty. These results hence support the use of hemoglobin and WCC as simple, inexpensive, and routinely available clinical indicators of systemic inflammation and age-associated immune system decline associated with frailty.

The 13 independent predictors selected in the final regression model represent an essential set of salient clinical risk indicators of prefrailty and frailty. It is noteworthy that these frailty risk factors are reflective of multiple system involvements for frailty. They include psychosocial, central nervous system (CNS) mood and sensory, cardiovascular, respiratory, renal, nutritional, and immune elements, in keeping with current understanding of the multicausation of frailty. The weighted scores assigned to each risk factor suggest stronger elements of CNS mood, sensory, and nutritional-immune involvements. The combined weight was 9 of a total of 21 for CNS mood and sensory involvement, and 4 of 21 for nutritional-immune involvement.

The FRI scores predicted frailty in this elderly population well: a greater number of risk factors and a higher risk score identified more individuals with frailty, and predicted a greater risk of developing functional dependency, hospitalization, and impaired quality of life. Indeed in this population, the FRI was comparable to the CHS Frailty scale and the FRAIL scale in predicting these adverse health outcomes. All the instruments have the ability to categorize individuals

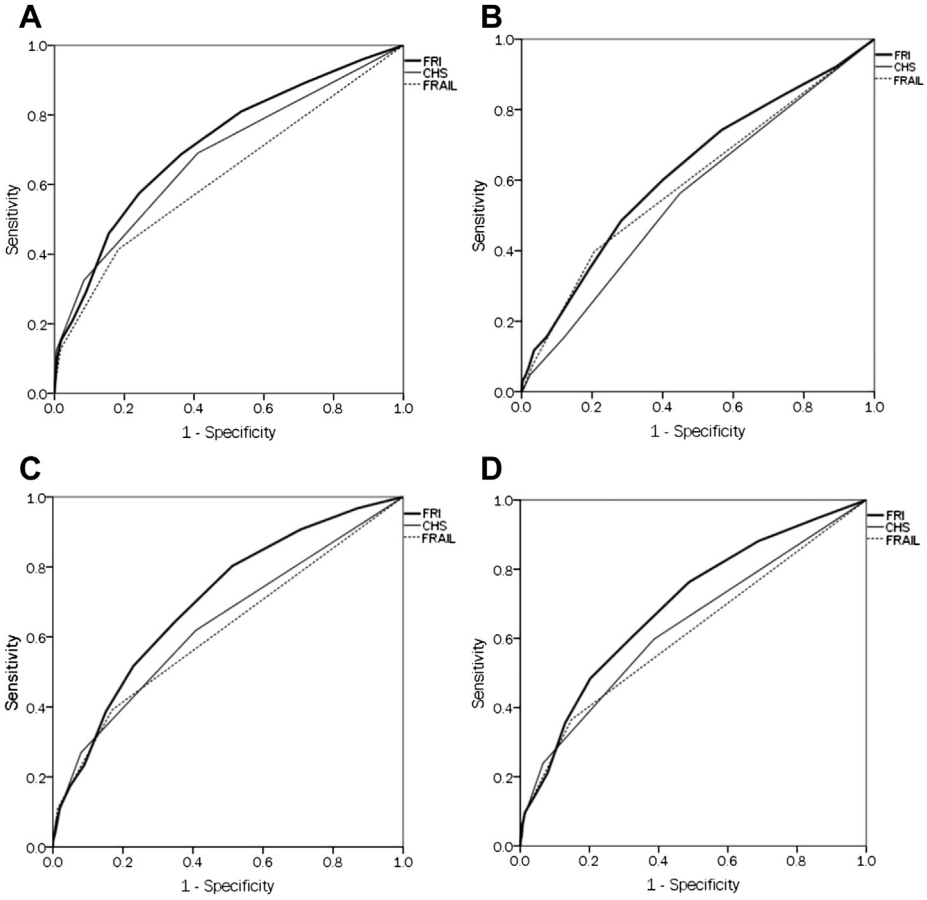

Fig. 3. ROC analyses of Frailty Risk Scale, CHS Frailty Scale, and FRAIL scale predicting IADL-ADL dependency (A), hospitalization (B) and lowest quintile SF12-PCS quality of life (C), and all adverse health outcomes (D).

as prefrail or frail at one point in time; however, the FRI with its continuous scores has the additional advantage of greater sensitivity in assessing change in risks over time.

It is possible that inclusion of additional factors, such as measures of lean muscle mass, inflammatory markers, or homocysteine levels may further improve the predictive power of the frailty risk score. These are generally not routinely available in primary care settings, but they may make it more useful in hospital-based settings. Another limitation is that the FRI has not been externally evaluated on mortality and institutionalization, and these should be evaluated in future studies. Comparison of frailty prevalence in this study with other studies using the CHS criteria for frailty may be limited by modifications to the operational definitions used; for example, to define weakness, dominant knee extension instead of handgrip strength was used in this study. However, these modifications do not affect the construct and criterion validity of the FRI in this study. Finally, non-Chinese ethnicity was associated with greater prevalence of frailty; the prevalence of many frailty-related risk factors are known to be greater among Malays and Indians, and it is possible that the risk predictor components and weights for FRI score may not be the same in different ethnic groups. The numbers and proportions with Malay and Indian ethnicities in this study sample were too small to permit stratified analysis by ethnic groups. However, we noted in the whole sample analysis that ethnicity in the presence of other risk variables was not selected as a significant risk variable in the FRI.

The FRI may be used routinely in primary care settings as a simple clinical risk indicator tool for frailty among elderly persons, and also as a compound variable to adjust for risk factors in research. Existing frailty scales such as the FI-CGA and the MPI-CGA are relatively resource-intensive prognostic tools useful in hospital geriatric settings for assessing mortality risks or need for nursing home care. Other brief screening tools, such as FRAIL and GFS, may be useful for identifying frail individuals in primary care, but the presence of frailty risk factors need to be further assessed for intervention purposes. In this context, the FRI is thus a useful rapid assessment tool to identify vital body system deficits underlying the frailty syndrome. The FRI does not replace other briefer screening tools to identify individuals with frailty, but is most useful as a secondary tool that classify patients as prefrail or frail to target specific risks for monitoring or intervention purposes.

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