의학석사 학위논문

한국 노인에서의 새로운 노쇠 척도 개발: 기존의 형질 노쇠 모델과의 비교

Developing a new frailty index for Korean elderly population: Comparison of outcome and prevalence of frailty with existing phenotype models

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정 희 원

A thesis of the Master's degree

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Developing a new frailty index for Korean elderly population: Comparison of outcome and prevalence of frailty with existing phenotype models

by

Hee-Won Jung

A thesis submitted to the Department of Internal Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Internal Medicine at Seoul National University College of Medicine

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학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무

본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

3. 서울대학교의 의무

① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

② 서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문 제목 : Prevalence and Outcomes of Frailty in Korean Elderly Population:

Comparisons of a Multidimensional Frailty Index with Two Phenotype Models

학위구분: 석사

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Abstract

Background: Frailty is related to adverse outcomes in the elderly. However, current status and clinical significance of frailty has not been evaluated for the Korean elderly population. We aimed to investigate the usefulness of established frailty criteria for community-dwelling Korean elderly. We also tried to develop and validate a new frailty index based on a multidimensional model.

Methods: We studied 693 participants of the Korean Longitudinal Study on Health and Aging (KLoSHA). We developed a new frailty index (KLoSHA Frailty Index, KFI) and compared predictability of it with the established frailty indexes from the Cardiovascular Health Study (CHS) and Study of Osteoporotic Fracture (SOF). Mortality, hospitalization, and functional decline were evaluated.

Results: The prevalence of frailty was 9.2% (SOF index), 13.2% (CHS index), and 15.6% (KFI). Frailty status by CHS and KFI correlated with each other, but SOF did not correlate with KFI. During the follow-up period (5.6 ± 0.9 years), 97 participants (14.0%) died. Frailty defined by KFI predicted mortality better than CHS index (c-index: 0.713 and 0.596, respectively; $p<0.001$, better for KFI). In contrast, frailty by SOF index was not related to mortality. The KFI showed better predictability for following functional decline than CHS index (area under the receiver-operating characteristic curve was 0.937 for KFI and 0.704 for CHS index, $p=0.001$). However, the SOF index could not predict subsequent functional decline. Frailty by the KFI (OR=2.13, 95% CI 1.04-4.35) and CHS index (OR=2.24, 95% CI 1.05-4.76) were significantly associated with hospitalization. In contrast, frailty by the SOF index was not significantly correlated with hospitalization (OR=1.43, 95% CI 0.68-3.01).

Conclusions: Prevalence of frailty was higher in Korea compared to previous studies in other countries. A novel frailty index (KFI), which includes domains of comprehensive geriatric assessment, is a valid criterion for the evaluation and prediction of frailty in the Korean elderly

population.

Keywords: Aging, Frailty, Mortality
Student number: 2012 – 21716

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Introduction

Frailty is a state of decreased homeostatic capacity against stress in older adults and reflects physiological age rather than chronological age. Frailty is also called as a state of homeostenosis, thereby known as the core of geriatric syndrome. Because prevalence and severity of frailty is increased with aging, frailty status widely overlaps with functional impairment and comorbidity. However, frailty has its independent features and prevalence, with some people showing phenotypic frailty without functional impairment or comorbidity [1]. With impaired homeostasis, frailty is well known as an independent risk factor for subsequent mortality, institutionalization, and morbidities such as fall, incontinence, and immobility [2,3].

Korea is known for one of the most rapidly aging country in the world [4]. Therefore, frailty has been a critically important public health problem due to its self-aggravating character and socio-economic burden. However, there is limited evidence of the prevalence and outcome for frailty in Korea. In addition, to our knowledge, there was no validated criterion of frailty for use in the Korean population, although the 'Korean frailty index' [5] showed some correlation with Cardiovascular Health Study (CHS) frailty index. All the more, validity was not evaluated through outcome measures in 'Korean frailty index'.

Although diverse conceptual models of frailty have been reported, the definition of frailty remains controversial [6]. Previous studies presented various diagnostic criteria for frailty [1,2,7,8], from a simple question appropriate for busy clinical settings to complex models more suitable for research. There have been attempts to diagnose frailty through phenotype model [1]. On the other hand, a model of the accumulation of deficit [8] is advocated by another group. Recently, a multidimensional model of frailty (Multidimensional Prognostic Index, MPI)

showed substantial validity [9].

The concept of phenotype model of frailty is based on clinical phenotype of frailty, consequently trying to diagnose frailty by operational diagnostic criteria. The phenotype model of CHS frailty index, which was most widely known for frailty criteria, was originally constructed from an epidemiological study, contains fortuitously chosen items from CHS study such as an activity questionnaire that is not typically used in clinical geriatric evaluation.

Two later models for frailty have a quantitative feature and use information acquired from a comprehensive geriatric assessment (CGA). The concept of accumulation of deficit model is quantifying severity of frailty with score (0 to 1) by numerous variables, usually measured from CGA. The accumulation of deficit model emphasizes the connected features of clinical deficits [10], assuming that model stability of frailty index can be established by increasing the number of variables (e.g. 30 or more variables). This model is known for its strong predictability for mortality and functional outcome in a community setting. On the other hand, MPI was composed by counting number of impaired domains in hospital based CGA. The MPI has substantial predictability for short term mortality in patients admitted to geriatric ward [9]. Moreover, the MPI was superior to the accumulation of deficit model and operational criteria in predicting the mortality of hospitalized patients [9]. Nevertheless, the validity of the MPI was less clear for functional outcome.

On these backgrounds, we aimed to develop and validate a new frailty index having characteristics of MPI with variables of CGA for Korean elderly to fill this unmet need of frailty in Korea. Thereafter we comprehensively evaluated the prevalence and adverse outcomes of frailty in community-dwelling older adults in Korea using newly developed frailty index and established frailty criteria. Furthermore, we compared the predictability for clinical outcome

from this novel index with the existing phenotypic frailty criteria

Materials and Methods

Study subjects

The Korean Longitudinal Study on Health and Aging (KLoSHA) has been described in detail in the literature [11,12]. Briefly, KLoSHA was a population based prospective cohort study of 992 Koreans 65 years or older residing in the city of Seongnam. The KLoSHA subject group consists of 714 randomly sampled individuals 65 years or older reflecting general elderly population and 278 volunteers 85 years or older. The baseline study was conducted from September 2005 to September 2006 in the Seoul National University Bundang Hospital (SNUBH). This study was conducted according to the Declaration of Helsinki. The Institutional Review Board of SNUBH approved the study protocol. Written informed consent was obtained from all subjects.

Among the 992 subjects, 693 participants underwent evaluation including the Short Physical Performance Battery (SPPB) and the handgrip strength test. Of the 693 subjects, 442 participants completed the 5-year follow up evaluation from May 2010 through March 2012. The reasons for follow up loss were unavailable contact (N=17), refusal of recommended follow-up tests (N=144), and death before follow up evaluation (N=90).

The baseline characteristics of the subjects who lost to follow up were compared with the subjects who completed the follow up. Subjects who lost to follow up were older, more frail, cognitively worse, and more functionally dependent (data not shown).

For external validation of KFI, existing CGA dataset of 291 consecutive patients of 65 or older who admitted to SNUBH from October 2011 to July 2012 for elective operation was used.

Baseline geriatric examination

The baseline examination of KLoSHA includes a broad range of geriatric evaluations. The complete list of evaluation items has been described previously [12].

Functional status

Activities of daily living (ADL) were assessed by the Korean Activities of Daily Living (K-ADL) scale, which includes evaluation of dressing, bathing, eating, getting out of bed, and using the toilet, with score ranging from 7 to 21 points (worse by increasing score). The instrumental ADL was evaluated using the Korean Instrumental Activities of Daily Living (K-IADL) scale, from 0 to 10 points, concerning grooming, housework, meal preparation, bathing, going to places outside the home, using transportation, shopping, managing money, and making phone calls (worse by increasing score).

Body composition, physical activity and performance

To assess body composition, a bioimpedence analysis with Inbody 3.0 (Biospace, Seoul, Korea) was performed with measurements of height and weight. Physical activity was measured by the Baltimore Longitudinal Study of Aging (BLSA) Activities Questionnaire [13]. Physical function was measured by the SPPB [14]. SPPB included sitting balance, stand up from seated state, and usual gait speed, with 0 to 4 points for each component (better for higher scores). Total score of SPPB was calculated. Isometric grip strength was assessed using a handgrip dynamometer (JAMAR hydraulic hand dynamometer, Sammons Preston, Bolingbrook, IL, USA).

Cognition and mood

Among many scales used in KLoSHA, the authors used the Korean version of the Geriatric Depression Scale (GDS-K), the Center for Epidemiological Studies depression (CES-D) scale [15], and the Korean Mini-Mental State Examination (K-MMSE) [16].

Frailty indexes

CHS frailty index

We used a modified version of the original CHS frailty index (CHS index) [1], which has been well validated. Frailty was defined by the following components: (1) unintentional weight loss of 3 kg or more for 6 months; (2) weakness of handgrip strength, ranking in the lowest quintile of the study population adjusted for body mass index; (3) exhaustion, shown by answers to the CES-D scale questions “I felt that everything I did was an effort” and “I could not get going” that were rated "moderate amount to most of the time during the last week"; (4) slowness, determined by a usual walking speed of 0.6 m/s or less; and (5) low physical activity, ranked in the lowest quintile (400 or less Kcal per week) on the BLSA Activities Questionnaire. The subjects having a score of 0 were considered robust, 1-2 indicated prefrail, and ≥ 3 indicated frail condition.

Study of Osteoporotic Fracture (SOF) frailty index

A modified SOF frailty index (SOF index) [2] was used with the following components: (1) unintentional weight loss of 3 kg or more for 6 months; (2) inability to stand from a chair 5 times; (3) reduced energy level indicated by answering “no” to the question “Do you feel full of energy?” on the GDS-K. Subjects having none of these components were considered to be

robust, those having 1 component were considered to be prefrail, and those having 2-3 components were considered to be frail.

KLoSHA frailty index

We intended to develop a multidimensional frailty index to reflect domains of CGA including physical function, physical performance, cognitive function, mood, and nutritional status. To increase dynamic range and discriminability of the new frailty index, applying weighting for each domain by its clinical significance was planned, rather than simple summation used in accumulation of deficits model. Accordingly, we selected the variables in KLoSHA that reflect these domains and show statistical significance for predicting mortality in the preliminary analysis. Among the variables, SPPB, K-MMSE, serum albumin level, K-ADL and K-IADL were selected. On the other hand, GDS-K was excluded because it failed to show statistical significance for mortality by neither continuous nor categorical fashion. The cut-off points for the K-MMSE [10] score were adapted from the literature. The weighting values of each variable were defined using the coefficients of the Cox proportional hazard model. Considering the intrinsic redundancy of the frailty model, unadjusted coefficients were used. A KLoSHA frailty index (KFI), total score of 1, was made (Table 1,2). Thereafter, cut-off values for prefrail ($\geq$0.2) and frail ($\geq$0.35) were defined by distributions of frailty index and clinical frailty scale of another study [8] for comparisons between KFI with other phenotype models of frailty. These cutoffs were well associated with expected outcomes for prefrail status (predictability for 5 year functional decline – sensitivity 0.95, specificity 0.53) and frail status (predictability for 5 year mortality – sensitivity 0.42, specificity 0.88).

Outcome measures

All of the participants were flagged for mortality at the National Statistical Office of Korea, which provided data for the date and cause of all deaths occurring until the end of December 2011. We added the mortality data from National Statistical Office of Korea to our dataset using each individual identifier. Functional decline at follow-up was defined as an increment in the K-ADL score. The data on hospitalization after the initial examination was gathered by patient interview at the follow-up assessment.

Table 1. Predictability of individual variables for death, by Cox proportional hazard analysis.

		β	HR	95% CI
12-total SPPB score		0.22	1.24	1.17- 1.32
K-ADL		0.19	1.20	1.10- 1.31
K-IADL		0.25	1.28	1.21- 1.36
Low albumin		0.78	2.18	1.46- 3.25
K-MMSE	21-24	0.22	1.24	0.73- 2.10
	18-20	0.14	1.15	0.52- 2.58
	11-17	1.35	3.85	2.22- 6.68
	1-10	2.39	10.92	5.56- 21.45

Table 2. Composition of the KLoSHA frailty index.

	Scoring	**Value**	Weighting	Score
SPPB	12-SPPB score	12	0.217	2.604
K-ADL score	Total score	21	0.185	3.885
K-IADL score	Number of impaired components	10	0.248	2.480
K-MMSE score	0 (25-), 0.25 (21-24), 0.5 (18-20),	1	2.391	2.391
Albumin	1 (0-4 g/dL), otherwise 0	1	0.780	0.780
Divide				12.140
Total				1.000

Higher scores in each domain and total frailty index denote worse states.

Statistical analysis

We used an independent t-test or analysis of variance (ANOVA) for continuous variables and $\chi 2$ test for discrete variables to evaluate the characteristics of the participants. Cox proportional hazards models were used to assess the associations between variables and death. The appropriateness of the Cox models was checked by log-log plot. The weighting factor of the KFI was derived from the coefficients of the Cox proportional hazards models. The variables included in fully adjusted Cox proportional hazards models were selected from the baseline data. We used Harrell's c-index [17] for each frailty index to compare the capability of discrimination for mortality. For KFI, bootstrapping of the total study sample was performed 1000 times, and the c-index was calculated. The linear correlation between each index was assessed with Spearman's coefficient. The effect of frail status on subsequent hospitalization and functional decline was evaluated by logistic regression analysis. Receiver operating characteristic (ROC) curves were made with each index and compared for functional decline and hospitalization. The statistical analysis was performed using STATA 12.0 (StataCorp, College Station, TX, USA)

Results

Baseline characteristics and frailty status by each index

The baseline characteristics, including the anthropometric information, comorbidity, and functional status of 693 subjects, are shown in table 3 and 4. The mean age was 75.9 (SD 8.9) years, and 352 subjects (50.8%) were female. Among the subjects, 143 (20.6%) were oldest-old (≥85 years old), 117 (16.9%) were old-old (75 - 84 years old), and 433 (62.5%) were young-old (65 - 74 years old).

Among the 621 subjects who were evaluated for the CHS index, 82 (13.2% total; 19.2% female, 7.3% male) were frail, and 369 (59.4% total; 60.6% female, 58.3% male) were prefrail. In the SOF index of 663 subjects, 61 (9.2% total; 9.9% female, 8.5% male) were frail, and 328 (49.5% total; 49.1% female, 49.8% male) were prefrail. The KFI was calculated for 668 subjects, showing 104 frail (15.6% total, KFI≥0.35; 22.2% female, 9.0% male) and 287 prefrail (43.0% total, 0.20≤KFI<0.35; 44.3% female, 41.6% male).

Table 3. Comparisons of demographic, anthropometric and laboratory data in examinees between dead or alive during the follow-up period.

	Alive	**N=596**	**Dead**	**N=97**	***p*-value**
Age (years)	73.39	(7.66)	82.15	(8.82)	**<0.001**
Sex (Female)	311	(52.20)	41	(42.30)	0.070
Body mass index (Kg/m2)	24.25	(3.13)	23.00	(3.48)	**0.001**
Height (Cm)	157.68	(0.05)	158.36	(9.68)	0.530
Skeletal muscle mass (Kg)	40.04	(7.62)	39.49	(8.53)	0.551
Systolic BP (mmHg)	132.30	(17.16)	133.54	(19.87)	0.563
Diastolic BP (mmHg)	83.22	(10.47)	82.38	(12.48)	0.476
Cerebrovascular disease	58	(9.70)	10	(10.3)	0.859
Cardiovascular disease	276	(46.30)	47	(48.50)	0.695
Cancer history	42	(7.00)	9	(9.30)	0.435
Hypertension	420	(70.50)	70	(72.20)	0.734
Diabetes	147	(24.70)	28	(28.90)	0.377
Hemoglobin (g/dL)	13.94	(1.43)	13.12	(1.39)	**<0.001**
Albumin (g/dL)	4.13	(0.23)	4.04	(0.29)	**0.004**
Cholesterol (mg/dL)	203.36	(38.25)	192.15	(33.55)	**0.007**
HDL-cholesterol (mg/dL)	60.48	(15.00)	58.99	(15.83)	0.371
Folate (ng/mL)	13.81	(17.29)	11.57	(12.84)	0.222
Hemoglobin A1C (g/dL)	6.05	(0.84)	6.03	(0.86)	0.851
Creatinine (mg/dL)	1.10	(0.23)	1.26	(0.53)	**0.005**
ESR (mm/hr)	18.69	(12.68)	23.45	(15.53)	**0.005**
Ferritin (ng/mL)	118.84	(122.78)	121.63	(93.27)	0.832
C-reactive protein (mg/dL)	0.23	(0.72)	0.26	(0.57)	0.728
Bilirubin (mg/dL)	0.84	(0.37)	0.82	(0.40)	0.757
ALT (mg/dL)	23.29	(18.17)	18.58	(10.47)	**0.014**
AST (mg/dL)	26.21	(16.74)	24.59	(7.89)	0.354
ALP (mg/dL)	75.68	(24.06)	84.59	(32.76)	**0.012**
SPPB, Balance	3.44	(0.97)	2.78	(1.34)	**<0.001**
SPPB, Walking speed	2.93	(1.03)	2.29	(1.16)	**<0.001**
SPPB, Seat standing	2.73	(1.20)	2.01	(1.24)	**<0.001**
12-total SPPB score	2.78	(2.58)	4.91	(3.13)	**<0.001**
K-ADL score	7.11	(0.74)	7.60	(1.92)	**0.016**
K-IADL score	12.37	(3.96)	15.77	(5.60)	**<0.001**
GDS-K score	10.77	(7.26)	12.01	(6.69)	**0.125**
K-MMSE score	24.17	(4.10)	20.63	(6.50)	**<0.001**
Education (years)	7.81	(5.68)	7.25	(5.65)	0.371

CHS frailty index	1.19	(1.06)	1.72	(1.01)	**<0.001**
SOF frailty index	0.69	(0.64)	0.59	(0.63)	0.457
KLoSHA frailty index	0.25	(0.10)	0.34	(0.15)	**<0.001**

Abbreviations: ASM/ht^2-appendicular skeletal muscle mass per square meter height, BP-blood pressure, HDL-cholesterol-high density lipoprotein cholesterol, ESR-erythrocyte sedimentation rate, ALT-alanine aminotransferase, AST-aspartate aminotransferase, ALP-alkaline phosphatase, SPPB-Short Physical Performance Battery, K-ADL score-Korean Activity of Daily Living score, K-IADL score-Korean Instrumental Activity of Daily Living score, GDS-K score-Korean version of the Geriatric Depression Scale score, K-MMSE score- the Korean Mini-Mental State Examination score, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture, KLoSHA-Korean Longitudinal Study on Health and Aging

Data are presented as the mean (SD) or number (%)

Frailty status was defined by KLoSHA frailty index, of 0.35 or more considered to be frail, 0.20 – 0.35 to be prefrail and less than 0.20 to be robust.

Table 4. Comparisons of baseline characteristics between robust, prefrail or frail people.

	Robust	**N=277**	**Pefrail**	**N=287**	**Frail**	**N=104**	***p*-value**
Age (years)	70.45	(5.71)	75.21	(7.92)	81.96	(7.98)	**<0.001**
Sex (Female)	112	(40.43)	148	(51.39)	74	(71.15)	**<0.001**
Body mass index (Kg/m2)	24.43	(2.94)	23.96	(3.35)	23.65	(3.58)	0.084
Height (Cm)	160.02	(8.65)	157.39	(8.63)	151.84	(9.38)	**<0.001**
Skeletal muscle mass (Kg)	42.17	(7.78)	39.22	(6.95)	35.59	(7.69)	**<0.001**
Systolic BP (mmHg)	132.85	(17.82)	131.46	(17.42)	135.18	(16.50)	0.170
Diastolic BP (mmHg)	83.67	(10.34)	82.49	(10.50)	83.75	(12.12)	0.357
Cerebrovascular disease	12	(4.33)	37	(12.89)	16	(15.38)	**<0.001**
Cardiovascular disease	127	(45.85)	140	(50.54)	43	(41.35)	0.416
Cancer history	25	(9.3)	20	(6.97)	4	(3.85)	0.214
Hypertension	133	(63.03)	154	(70.97)	52	(72.22)	0.147
Diabetes	45	(16.24)	55	(19.16)	14	(13.46)	0.372
Hemoglobin (g/dL)	14.31	(1.38)	13.75	(1.32)	12.94	(1.45)	**<0.001**

Albumin (g/dL)	4.19	(0.17)	4.10	(0.24)	4.00	(0.34)	**<0.001**
Cholesterol (mg/dL)	202.24	(36.48)	201.37	(38.80)	202.42	(38.54)	0.953
HDL-cholesterol (mg/dL)	61.48	(15.66)	59.88	(14.17)	59.76	(16.47)	0.393
Folate (ng/mL)	13.02	(10.78)	14.85	(21.03)	9.73	(7.74)	**0.017**
Hemoglobin A1C (g/dL)	6.11	(0.88)	6.01	(0.77)	6.00	(0.92)	0.324
Creatinine (mg/dL)	1.12	(0.21)	1.12	(0.36)	1.14	(0.35)	0.818
ESR (mm/hr)	17.22	(12.01)	19.03	(13.12)	25.21	(15.06)	**<0.001**
Ferritin (ng/mL)	126.82	(153.26)	119.55	(95.30)	95.42	(62.98)	0.079
C-reactive protein (mg/dL)	0.22	(0.54)	0.22	(0.54)	0.35	(1.29)	0.237
Bilirubin (mg/dL)	0.86	(0.37)	0.84	(0.39)	0.76	(0.33)	0.073
ALT (mg/dL)	26.53	(16.48)	26.07	(17.78)	24.82	(7.46)	0.655
AST (mg/dL)	24.78	(15.05)	22.64	(21.10)	17.90	(8.46)	**0.003**
ALP (mg/dL)	73.57	(21.23)	75.87	(26.57)	86.48	(29.21)	**<0.001**
SPPB, Balance	3.88	(0.37)	3.36	(0.90)	2.01	(1.35)	**<0.001**
SPPB, Walking speed	3.48	(0.71)	2.70	(0.96)	1.63	(0.87)	**<0.001**
SPPB, Seat standing	3.54	(0.75)	2.45	(1.11)	1.31	(0.94)	**<0.001**
12-total SPPB score	1.10	(1.23)	3.48	(2.05)	7.05	(2.35)	**<0.001**
K-ADL score	7.02	(0.13)	7.05	(0.25)	7.64	(1.91)	**<0.001**
K-IADL score	9.09	(6.45)	11.19	(7.44)	14.99	(6.51)	**<0.001**
GDS-K score	0.43	(0.85)	1.08	(1.29)	4.39	(3.10)	**<0.001**
K-MMSE score	26.48	(1.94)	23.68	(3.31)	17.20	(5.31)	**<0.001**
Education (years)	8.62	(5.60)	8.21	(5.48)	4.94	(5.39)	**<0.001**
CHS frailty index	0.60	(0.58)	0.96	(0.55)	1.36	(0.53)	**<0.001**
SOF frailty index	0.68	(0.60)	0.67	(0.65)	0.71	(0.69)	0.858
KLoSHA frailty index	0.15	(0.03)	0.26	(0.04)	0.49	(0.13)	**<0.001**

Abbreviations: ASM/ht^2-appendicular skeletal muscle mass per square meter height, BP-blood pressure, HDL-cholesterol-high density lipoprotein cholesterol, ESR-erythrocyte sedimentation rate, ALT-alanine aminotransferase, AST-aspartate aminotransferase, ALP-alkaline phosphatase, SPPB-Short Physical Performance Battery, K-ADL score-Korean Activity of Daily Living score, K-IADL score-Korean Instrumental Activity of Daily Living score, GDS-K score-Korean version of the Geriatric Depression Scale score, K-MMSE score- the Korean Mini-Mental State Examination score, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture, KLoSHA-Korean Longitudinal Study on Health and Aging

Data are presented as the mean (SD) or number (%)

Spearman's coefficient between the CHS index and the SOF index was 0.252 (p<0.001), that between the CHS index and the KFI was 0.487 (p<0.001), and that between the SOF index and KFI was -0.003 (p=0.949).

During a mean follow-up of 5.57 years (SD=0.93), 97 subjects died, 139 experienced hospitalization, and 18 showed functional decline. The subjects with follow-up loss were older (p<0.001) and more frail at the baseline evaluation (p<0.001 with KFI, p=0.001 with CHS index). They had a higher GDS-K score (p=0.001), more impaired K-ADL (p=0.002) and K-IADL (p<0.001), and a worse SPPB score (p<0.001).

The correlations between KFI and key variables or age are presented in figure 1 and 2, respectively. In the subjects who were classified as frail by the 3 indexes, the SPPB score, K-IADL score, subjective health status, and duration of education were worse (all p<0.05). Frail subjects by the CHS index and the KFI were older, had lower muscle mass, albumin levels, and MMSE scores (all p<0.05).

Figure 1. The distributions of each KFI-component variable by KFI and fractional polynomial prediction plots. The shaded area denotes a 95% confidence interval for the prediction curve. (A) 12-SPPB score (B) K-ADL score (C) K-IADL score (D) K-MMSE score (E) albumin (mg/dL).

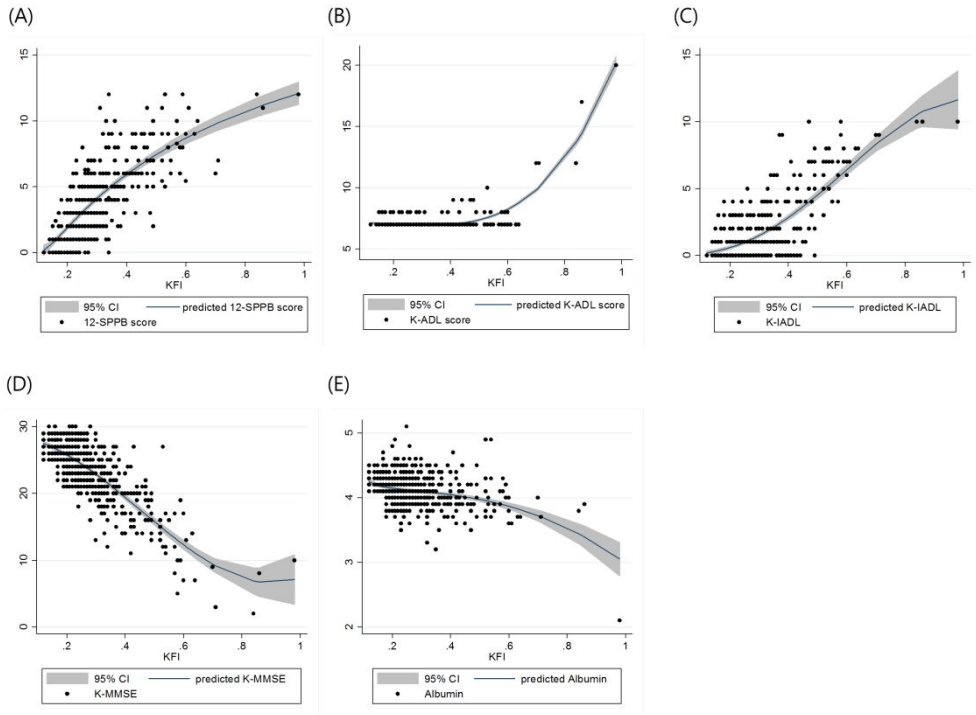
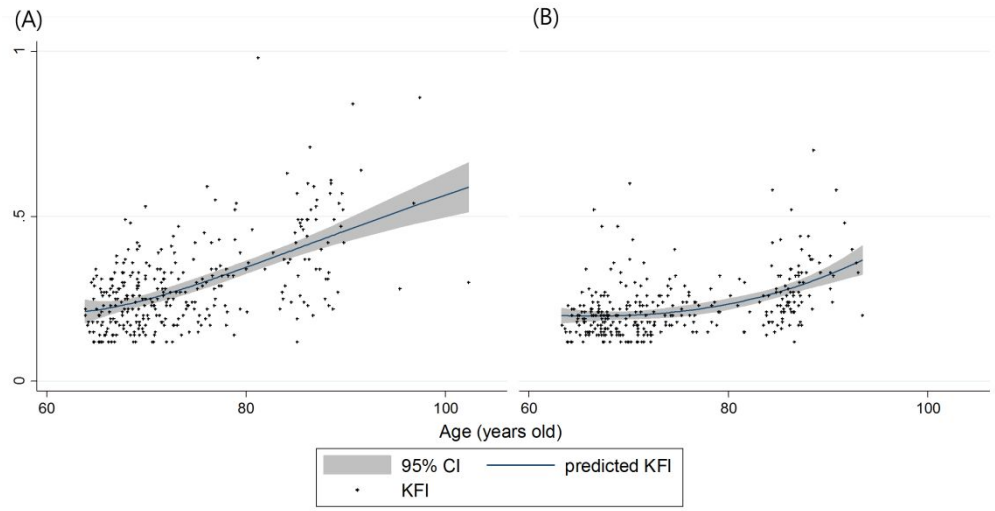


Figure 2. The distributions of KFI by age and fractional polynomial prediction plots plotted by sex, (A) female, (B) male. The shaded area denotes a 95% confidence interval for the prediction curve.



Predictability of clinical outcomes by each index

Outcomes including mortality, functional decline, and hospitalization were evaluated. As shown in table 2, the SPPB score, K-ADL score, low albumin, and K-MMSE were related to mortality. The frailty status defined by the KFI and the CHS index were correlated with mortality, while frailty from the SOF index was not (Table 5). Harrell's c-indexes of each frailty index are shown in table 6, and there is statistically significant difference between the KFI and CHS index (p<0.001), KFI showing better predictability for mortality.

Table 5. Unadjusted and adjusted hazard ratio for the mortality according to the frailty status from each frailty index

	HR	95% CI
Unadjusted Cox proportional hazard analysis		
KLoSHA index (Frail)	7.23	4.01 - 13.05
CHS index (Frail)	4.05	1.62 - 10.16
SOF index (Frail)	0.67	0.28 - 1.58
Fully adjusted Cox proportional hazard analysis*		
KLoSHA index (Frail)	2.18	1.07 - 4.45
CHS index (Frail)	1.33	0.50 - 3.60
SOF index (Frail)	0.69	0.29 - 1.67

*Adjusted by age, hemoglobin, cholesterol, creatinine, erythrocyte sedimentation rate, alanine aminotransferase, alkaline phosphatase

Reference variable: Robust state of each frailty index

Abbreviations: HR-hazard ratio, 95% CI-95% confidence interval, KLoSHA-Korean Longitudinal Study on Health and Aging, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture

Table 6. Comparisons of predictability for mortality by frailty status from each frailty index

	C-index	*p*-value †	95% CI
KLoSHA index *	0.713		0.656- 0.770
CHS index	0.596		0.549- 0.642
SOF index	0.542		0.485- 0.598
KLoSHA index vs. CHS index		<0.001	
KLoSHA index vs. SOF index		<0.001	

*Bootstrapped 1000 times

† p-value for C-index difference

Abbreviations: 95% CI-95% confidence interval, KLoSHA-Korean Longitudinal Study on Health and Aging, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture

Functional decline was analyzed with the frailty index using a logistic regression model. Frailty assessed by the KFI and CHS indexes predicted subsequent functional decline, which was defined by 1 or more increments on the K-ADL score (Table 7). The association between the frailty index and hospitalizations was analyzed using a logistic regression model. Frailty from the KFI and CHS index was related to a subsequent hospitalization (Table 8).

Table 7. Impact of frailty status from each frailty index on subsequent functional decline

		OR	95% CI
KLoSHA index	Prefrail	4.06	0.42 -39.39
	Frail	148.00	18.54 -1181.72
CHS index	Prefrail	6.62	0.85 -51.87
	Frail	20.53	2.40 -175.80
SOF index	Prefrail	0.47	0.17 -1.32
	Frail	0.81	0.17 -3.82

Reference variable: Robust state of each frailty index

Abbreviations: OR-odds ratio, 95% CI-95% confidence interval, KLoSHA-Korean Longitudinal Study on Health and Aging, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture

Table 8. Impact of frailty status from each frailty index on following experience of hospitalization

		OR	95% CI
KLoSHa index	Prefrail	0.90	0.57 - 1.41
	Frail	2.13	1.04 - 4.35
CHS index	Prefrail	1.44	0.87 - 2.39
	Frail	2.24	1.05 - 4.76
SOF index	Prefrail	0.94	0.60 - 1.47
	Frail	1.43	0.68 - 3.01

Reference variable: Robust state of each frailty index

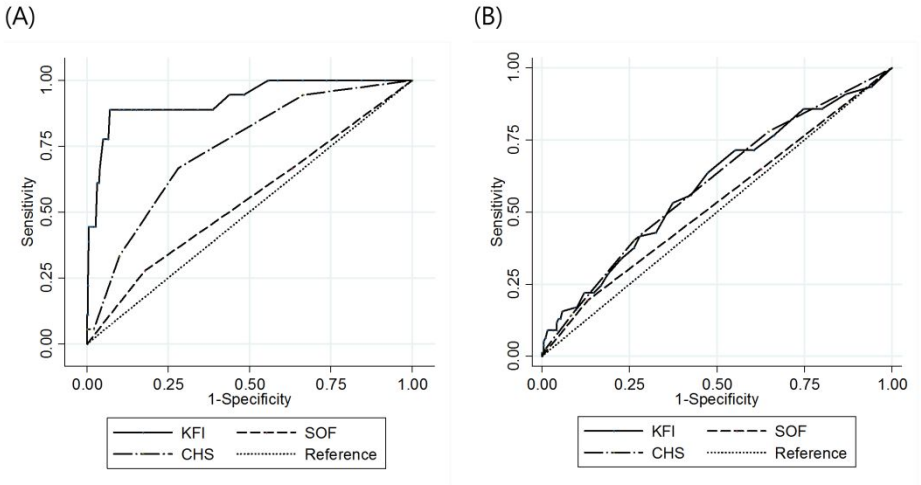
Abbreviations: OR-odds ratio, 95% CI-95% confidence interval, KLoSHA-Korean Longitudinal Study on Health and Aging, CHS-Cardiovascular Health Study, SOF-Study of Osteoporotic Fracture

The ROC curves for functional decline and hospitalization by each index are shown in figure 3. The KFI had a significantly larger area under the curve (AUC) for functional decline compared to the CHS and SOF indexes (AUC of ROC curve: 0.937, 0.704 and 0.565, respectively. Comparing each ROC curve, p=0.001 between KFI and CHS, p<0.001 between KFI and SOF, p=0.069 between CHS and SOF). The KFI and CHS showed no significant difference in the prediction of subsequent hospitalization.

Figure 3. ROC curves for (A) functional decline, (B) hospitalization.

(A) The area under the curve is 0.937 for KFI, 0.704 for CHS, and 0.565 for SOF; for the difference of each ROC curve, p=0.001 for KFI and CHS, p<0.001 for KFI and SOF, p=0.069 for CHS and SOF.

(B) The area under the curve is 0.543 for KFS, 0.560 for CHS, and 0.505 for SOF; for the difference of each ROC curve, p=0.639 for KFI and CHS, p=0.374 for KFI and SOF, p=0.180 for CHS and SOF.



External validation of KFI on mortality and functional outcomes

In the validation cohort dataset with CGA composed with patients undergoing elective surgery, mean age was 75.8 years (SD 5.7) and male were 56.4 percent. Baseline characteristics of the validation cohort were showed in table 9. Among these, KFI was calculated eventually revealing 32 (10.5%) robust, 175 (57.4%) prefrail, and 84 (27.5%) frail people. During the follow-up period (mean 389 days, SD 120.5), 39 (12.74%) patients died. Predictability of KFI on mortality was assessed by the same way performed in the present study, resulting Harrell's c-index of 0.71 (100x bootstrapped, 95% CI 0.62-0.79, $p<0.001$). Furthermore, the KFI could predict composite outcome (in hospital death during immediate post-op period or discharge to nursing facility) with AUC of ROC curve of 0.73 (95% CI 0.62-0.84, $p<0.001$).

Table 9. Comparison of demographic, laboratory and frailty status data between patients with and without mortality in validation cohort.

	Alive N=250	**Dead N=41**	***p*-value**
Age (years)	75.1 (5.00)	77.9 (6.59)	**0.016**
Gender (Female)	115 (45.3)	10 (24.4)	**0.036**
Body mass index (kg/m^2)	23.4 (3.24)	21.0 (3.21)	**< 0.001**
Cancer	129 (51.6)	19 (76.0%)	**0.021**
Laparoscopic surgery	181 (71.3)	5 (13.5)	**< 0.001**
Hemoglobin (g/dL)	12.4 (2.13)	11,7 (2.00)	0.088
Creatinine (mg/dL)	0.89 (0.41)	0.97 (0.45)	0.412
Protein (mg/dL)	6.5 (0.82)	6.4 (0.88)	0.524
Albumin (mg/dL)	3.8 (0.58)	3.5 (0.63)	**0.006**
AST (IU/L)	51.4 (146.9)	43.3 (43.1)	0.783
ALT (IU/L)	49.3 (142.5)	42.7 (53.1)	0.783
KLoSHA frailty index	0.31 (0.12)	0.43 (0.20)	**0.001**

Data are presented as mean (SD) or number (%).

Discussion

In this study, we developed a novel frailty index (KFI) scoring from 0 to 1. To the best of author's knowledge, applying weighting factors for an existing CGA component to create a frailty index is a novel approach. We also showed the prevalence and clinical outcomes of frailty, using existing and novel criteria among a population of Korean community-dwelling elderly people. The KFI showed better predictability in mortality and functional decline compared with the CHS index.

The prevalence of frailty in this study is higher than that in other studies conducted with Caucasian and Asian [18] populations. In the original CHS study [1], the prevalence of frailty was 7.3% for females and 4.9% for males. A study [19] conducted in China used a frailty index ranging from 0 to 1, and showed a frailty index pattern by age and sex similar to that in this study. Because the KLoSHA consists of 22% of volunteers aged 85 or older, the study population in this study is generally older than that in other cohort studies and may show an increased prevalence of frailty.

An effective frailty index should have the following characteristics [8]. It should be useful, simple, and brief for use in a clinical setting. The domains and characteristics of the KFI were originally chosen to enable automatic calculation from a previously prepared electronic medical record based on CGA data. Although it is cumbersome for primary physicians to use as brief screening test, clinicians can automatically obtain the KFI with CGA and predict the physiological age and quantified vulnerability of a patient.

A good frailty index should show a general demographic pattern of frailty. Using the KFI in KLoSHA, a gradually rising frailty index was observed with increasing age. The KFI of females

was greater than the age-matched KFI of males and never crossed (Figure 2). This phenomenon of more prevalent vulnerability in females is observed in many other studies of frailty [19,20]. Frailty has features independent of functional impairment or comorbidity, although it is broadly correlated with them. The KFI, ADL, and IADL share significant proportions, having vectors of functional impairment that reflect the phenotypic characteristics of frailty.

An effective frailty index may predict adverse outcomes, such as mortality, institutionalization, and functional decline. Using c-statistics, the predictive validity for mortality by the KFI is better than that from the CHS index, which has been validated effectively by larger studies [1,2,21]. Interestingly, CHS index lost its predictability for mortality in a fully-adjusted Cox proportional hazards model. By comparing the ROC curves for functional decline and hospitalization of the three indexes, the KFI predicted functional decline better than CHS index, and the KFI prediction for hospitalization was comparable with the prediction of the CHS index.

Although the SOF index was significantly correlated with the CHS index, it could not predict mortality, functional decline, and hospitalization contrary to results from previous studies [2,9]. In a search by the author, there was no report showing the validity of the SOF index in the Asian population. In this study, significant weight loss of 3 kg for 6 months was not related to mortality using the Cox-proportional hazard analysis (HR=0.912, 95% CI 0.713-1.167, p=0.465). Furthermore, only 22 subjects were unable to stand up from their seat 5 times without using their arms. Although the CHS index included the weight loss item, it showed superior predictability for outcome compared to the SOF index. This phenomenon may be explained by the low model stability of the SOF index because it is limited to three components. These findings indicate that the variables chosen in the SOF index may not be appropriate for the

elderly in Korea. Accordingly, clinicians should be cautious adopting frailty indexes validated in Caucasians for use with other ethnic groups.

Similar to other major studies of frailty, KLoSHA was not originally designed to assess frailty. Therefore, not all of domains routinely measured in CGA were included in KLoSHA. For this reason, authors used SPPB for physical performance and serum albumin level for nutritional status rather than originally intended timed get up and go test and mini-nutritional assessment (MNA), which can be acquired from CGA. Because SPPB is not usually performed as a part of CGA, further studies are needed to replace SPPB with another easier method such as timed get up and go test or usual gait speed for universal application of KFI.

This study has several limitations. There were many follow-up losses, especially for the 5-year follow-up examination, with poorer baseline characteristics identified in these subjects. Although we used complete government registry data for death occurrences, the unbalanced follow-up losses may weaken the validity of the follow-up data for functional status and hospitalization. Furthermore, follow-up examination was limited to 5 year later from baseline evaluation, impeding opportunity to assess geriatric outcomes including fall down, time of functional decline, and institutionalization. Due to the relatively small sample size, bootstrapping was used to cross-validate the c-index for the KFI, rather than a validation cohort. Consequently, the problem of over fitting cannot be completely ruled out. In addition, we used the unadjusted coefficients from Cox proportional hazards model as the weighting value for each component of KFI. Accordingly, this method might compromise the generalizability of the study findings to other population. However, external validation of KFI in a cohort of surgical patients showed predictability of mortality and functional outcomes. Also, KFI predicted functional decline better than CHS index and also could predict hospitalization, showed

performance beyond its expected data-driven ability for mortality prediction.

In conclusion, we showed the prevalence and outcome of frailty in Korea. Also, we devised a new multidimensional frailty index, which includes domains from the CGA. By comparisons with previously developed phenotype models, the KFI showed its validity as appropriate frailty assessment instrument for Korean elderly population.

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초 록

서론: 노쇠는 노인에서 유해한 예후와 관련되어 있는 노인 증후군이다. 비록 고령화 속도가 빠르지만 한국에서 노쇠의 진단 기준에 대한 연구는 부족한 실정이다. 이에 본 연구에서는 여러 노쇠 진단 기준을 한국의 지역사회 거주 노인에서 검증하며, 또한 다면성 모델에 의거하여 새로운 노쇠 척도를 수립하고자 하였다.

방법: Korean Longitudinal Study on Health and Aging (KLoSHA) 연구 코호트의 693명을 분석하였다. 새로운 노쇠 척도를 수립하였고 (KLoSHA Frailty Index, KFI), 기존에 알려진 Cardiovascular Health Study (CHS) 와 Study of Osteoporotic Fracture (SOF) 의 노쇠 진단기준과 함께 예후 예측 능력을 비교하였다. 예후 인자로 사망, 입원과 기능 저하를 평가하였다.

결과: SOF, CHS, KFI 등 진단방법에 따른 노쇠 여부는 서로 연관성을 보였으며, 각각의 Spearman's coefficient 는 -0.003 에서 0.487로 측정되었다. 추적 관찰 기간동안 (5.6 ± 0.9 년), 97 (14.0%) 명이 사망하였다. CHS 기준과 KFI에 따른 노쇠는 사망과 연관되어 있었으나 (c-index: 0.596 and 0.713, respectably; $p<0.001$, better for KFI) SOF 기준은 사망을 예측하지 못하였다. KFI 는 CHS 기준보다 기능 저하를 더 잘 예측하였지만 (AUC of ROC: 0.937 for KFI and 0.704 for CHS index, $p=0.001$), SOF 기준은 기능 저하를 예측하지 못하였다. KFI 와 CHS 기준에 따른 노쇠는 향후의 입원과 연관되어 있었으나 (HR=2.13, 95% CI 1.04-4.35 for KFI, HR=2.24, 95% CI 1.05-4.76 for CHS) SOF 기준에 따른 노쇠는 입원과 연관되지 않았다 (HR=1.43, 95% CI 0.68-3.01).

결론: 새로 노쇠 척도는 (KFI) 노인 포괄 평가 결과로부터 계산될 수 있으며, 한국 노인 인구에서 임상적으로 예후를 잘 예측할 수 있는 유용한 노쇠 평가 도구이다.

주요어: 노화, 노쇠, 사망
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