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Predictive Mortality Index for Community-Dwelling Elderly Koreans

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Abstract: There are very few predictive indexes for long-term mortality among community-dwelling elderly Asian individuals, despite its importance, given the rapid and continuous increase in this population. We aimed to develop 10-year predictive mortality indexes for community-dwelling elderly Korean men and women based on routinely collected clinical data.

We used data from 2244 elderly individuals (older than 60 years of age) from the southwest Seoul Study, a prospective cohort study, for the development of a prognostic index. An independent longitudinal cohort of 679 elderly participants was selected from the Korean Genome Epidemiology Study in Ansan City for validation.

During a 10-year follow-up, 393 participants (17.5%) from the development cohort died. Nine risk factors were identified and weighed in the Cox proportional regression model to create a point scoring system: age, male sex, smoking, diabetes, systolic blood pressure, triglyceride, total cholesterol, white blood cell count, and hemoglobin. In the development cohort, the 10-year mortality risk was 6.6%, 14.8%, 18.2%, and 38.4% among subjects with 1 to 4, 5 to 7, 8 to 9, and $\geq$10 points, respectively. In the validation cohort, the 10-year mortality risk was 5.2%, 12.0%, 16.0%, and 16.0% according to these categories. The C-statistic for the point system was 0.73 and 0.67 in the development and validation cohorts, respectively.

The present study provides valuable information for prognosis among elderly Koreans and may guide individualized approaches for appropriate care in a rapidly aging society.

(*Medicine* 95(5):e2696)

Abbreviations: 2hPG = 2-h plasma glucose after 75 g glucose loading, AUC = area under the curve, BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, FPG = fasting plasma glucose, Hb = hemoglobin, HDL = high-density lipoprotein, HDL-C = HDL-cholesterol, HR = hazard ratio, NRI = net reclassification improvement, SBP = systolic blood pressure, SE = standard error, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count, WC = waist circumference.

INTRODUCTION

The population of Asia is continuously growing and aging. Currently, Asia's population is estimated to be 4.2 billion and is expected to increase to about 5.9 billion by 2050.[1] Furthermore, the number of elderly Asians aged 65 years and older will grow 4-fold, from about 250,000,000 at present to about 1 billion by 2050.[1] Mortality prediction has pivotal importance for individualized care among elderly adults, who show considerable diversity in health status, functional limitations, and the benefits and risks of medication interventions. In the context of making clinical decisions, disregard of an individual's prognosis can lead to poor care among elderly patients. Older patients with a longer life expectancy may be more likely to benefit from cancer screening, as recent guidelines recommend screening among elderly individuals with life expectancies >5 years.[2,3] Recently, the 8th Joint National Committee recommended different targets for blood pressure control according to a patient's age.[4] Similarly, the American Diabetes Association and the European Association for the Study of Diabetes emphasized a patient-centered approach for glycemic control based on specific patient characteristics and disease factors.[5] Appropriate application of prognostic indices may offer an important role in moving beyond arbitrary age-based cutoffs in clinical decision-making in elderly patients.[6] However, most published clinical indexes provide short-term mortality prediction or describe mortality only among patients with specific diseases.[7–9] Furthermore, many studies have not been validated by other cohort data independent from the

Editor: Leonardo Roever.
Received: November 9, 2015; revised and accepted: January 12, 2016.
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Supplemental Digital Content is available for this article.
Author contributions: NHK conceived, designed and supervised the study, and wrote the first draft of the manuscript. SGK and SK helped with data analysis, supervised the study, and reviewed the manuscript critically. JHS and HJL collected the data and coordinated the study. HJC analyzed the data. JHY, HSC, and HJY supervised data collection and assisted with data interpretation. JAS, SHB, and DSC helped to design the study and reviewed the manuscript critically. CS designed the study and provided the validation data. KMC designed and supervised the study and reviewed the manuscript critically. KMC is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
This study was supported by the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C0133, KMC), by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP, NRF-2015R1A2A2A01003167), and research fund from the Korea Centers for Disease Control and Prevention (2001–347–6111–221, 2002–347–6111–221).
The authors have no conflicts of interest to report.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002696

original cohort samples.[10] Also, several indices require additional information, such as information about activities of daily living, which may not be routinely collected in health examinations or clinical settings.[11] Self-reported information, including diverse measures of functional status, has not been adequately standardized and is often not available in medical records or routine health examinations. In particular, most previous indices were produced and validated using white populations. Therefore, there have been very few reports for mortality prediction indices that are adequately validated by an independent long-term longitudinal cohort in a community-dwelling Asian elderly population.

In the present study, using 2 independent prospective cohort samples, we developed and validated a novel predictive mortality index based on routinely collected clinical data for community-dwelling elderly Korean men and women.

MATERIALS AND METHODS

Study Population

We analyzed follow-up data from the southwest Seoul (SWS) Study, a prospective cohort study of elderly Koreans residing in a metropolitan city. The subjects and methods of this cohort study were described elsewhere in detail.[12,13] Briefly, the study population was selected from 4 urban districts (Guro, Yangcheon, Gwanak, and Gangseo) located in the southwest area of Seoul. A total of 1737 apparently healthy individuals (between 60 and 95 years of age) participated in this survey in 1999. Detailed history taking and blood sampling were conducted by medical personnel of Korea University in regional senior welfare centers operated by the Seoul metropolitan government. All subjects provided informed consent before participating in the study, and the study had the approval of the local research ethics committee and adhered to the Declaration of Helsinki. Follow-up examinations were held in 2002, and an additional 873 subjects who had not participated in the first wave of the study were newly recruited. Each subject's vital status as of December 31, 2012 was determined after linking the cohort data with death certificate data from the Korean National Statistical Office. After excluding subjects younger than 60 years, those missing laboratory data and those with mismatched identification numbers, 2244 subjects were included in model development analysis.

Data from Korean Genome Epidemiology Study in Ansan city were used for independent validation of the development model. Detailed information on the study design and procedures were available in previous reports.[14] It is an ongoing population-based cohort study that began in 2001, and consisted of 5015 participants (2,521 men and 2,494 women aged 40–69 years) at baseline who underwent a comprehensive health examination. After a median follow-up of 10.7 years, each subject's vital status as of December 31, 2012 was determined after linking cohort data with death certificate data from the Korean National Statistical Office. To establish a validation dataset of elderly individuals, we included subjects who were older than 60 years at baseline. After excluding those with mismatched identification numbers and missing laboratory data, 679 subjects were included in model validation.

Data Collection

At baseline, participants in both cohort studies responded to an interviewer-administered questionnaire and underwent a comprehensive physical examination. Lifestyle characteristics, current smoking status, and alcohol consumption were categorized with yes/no response options. Subjects who engaged in regular exercise ($\geq$3 times/week, $\geq$30 min/session) during the previous month were defined as the exercise group. The presence of chronic illness, including diabetes, hypertension, and cardiovascular disease (CVD), was noted, as were prescribed medications. Height was measured to the nearest 0.1 cm using a fixed wall-scale measuring device. Weight was measured to the nearest 0.1 kg using an electronic scale that was calibrated before each measurement. Body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest 0.5 cm in a horizontal plane at the level of the umbilicus at the end of normal expiration.

Blood was drawn to measure fasting serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and complete blood cell count. Plasma glucose levels 2 hours after 75-g oral glucose loading were measured (2-h plasma glucose [2hPG]). Diabetes was defined by the American Diabetes Association criteria, using a 75-g oral glucose tolerance test (fasting plasma glucose [FPG] $\geq$126 mg/dL or 2hPG $\geq$200 mg/dL), and medical history (SI conversion factors: to convert glucose to mmol/L, multiply by 0.0555). Serum triglyceride and HDL-cholesterol (HDL-C) levels were determined enzymatically using a model 747 chemistry analyzer (Hitachi, Tokyo, Japan). The glucose oxidase method was used to measure plasma glucose levels.

Outcome

The primary outcome of interest was death from all causes. We measured 10-year mortality from the date of recruitment in the baseline examination until death, or until 31 December 2012, whichever occurred first.

Statistical Analysis

Baseline characteristics of the participants were analyzed and presented as mean $\pm$ SD, median with interquartile range, or frequency. Time-to-death analyses were performed using multivariate Cox proportional hazards regression models, and risks were reported as hazard ratios (HRs) with their 95% confidence intervals. The assumptions of proportionality were tested using log follow-up time interaction terms for each baseline variable and no violations were found.

To test the stability of our model, we used forward variable selection within multivariate Cox regression. Starting from the empty model, each step selected a predictor, and once included in the multivariate Cox model, yielded the maximum net reclassification improvement (NRI).[15] The selection procedure, which analyzed the available variables, stopped when no further statistically significant NRI was detected. The final predictors from both methods were the same: age, sex, smoking, systolic blood pressure (SBP), FPG, total cholesterol, white blood cell count (WBC), hemoglobin, and triglycerides. In addition, the continuous predictors in the regression model were classified as binary variables to create a point scoring algorithm. We assigned points to each risk factor by dividing their estimates by the lowest estimate and rounding to the nearest integer. Each point score was summed and total points were presented with approximate mortality risk.[16] The mortality risk (%) corresponding to total points was calculated using the mortality risk equation for 10 years, which was calculated using the baseline survival probability up to 10 years ($S\,[t] = 0.85298$)[15]. To test the external validity and calibration of the model, we applied the point scoring system to the validation cohort, thereby determining the risk score of each individual. For each cohort, we

TABLE 1. Baseline Characteristics of the Study Population

	Development, n = 2244	Validation, n = 679
Age	69.8 ± 5.6	63.8 ± 2.6
Men, N (%)	497 (22.2)	285 (42.0)
BMI, kg/m^2	24.6 ± 3.1	25.1 ± 3.1
WC, cm	85.9 ± 8.9	83.6 ± 7.9
SBP, mmHg	140.4 ± 20.9	128.1 ± 18.9
DBP, mmHg	84.7 ± 10.6	81.0 ± 10.8
FPG, mg/dL	102.6 ± 24.3	91.7 ± 24.2
2hPG, mg/dL	137.1 ± 55.2	151 ± 57
TG*, mg/dL	125 (93, 173)	148 (111, 199)
TC, mg/dL	199.4 ± 34.5	204.8 ± 37.3
HDL-C, mg/dL	54.4 ± 12.9	44.4 ± 10.0
WBC (count/uL)	6.1 ± 2.0	6.8 ± 1.8
Hb, g/dL	13.3 ± 1.3	13.5 ± 1.4
Smoking, N (%)	245 (10.9)	101 (14.9)
Alcohol, N (%)	373 (16.6)	61 (9.0)
Diabetes, N (%)	483 (21.5)	164 (24.2)
Hypertension, N (%)	1432 (63.8)	318 (47.0)
Mets, N (%)	1086 (48.5)	498 (73.3)

Data are presented as mean ± SD, or N (%). SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. 2hPG = 2-h plasma glucose after 75 g glucose loading, BMI = body mass index, DBP = diastolic blood pressure, FPG = fasting plasma glucose, Hb = hemoglobin, HDL-C = HDL-cholesterol, Mets = metabolic syndrome, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count, WC = waist circumference (count/uL).
* Median (1st quartile, 3rd quartile).

stratified the risk score into 4 categories and calculated 10-year mortality.

Discrimination was assessed by area under the curve (AUC) and C-statistic for survival data.[16,17] To determine the agreement between the predicted and observed risks, calibration was performed. The Hosmer-Lemeshow (HL) statistic with 9 d.f. was applied to test for calibration by dividing 10 predicted risk groups. Analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics of Study Subjects

In the development cohort, the mean age of the participants was 69.8 ± 5.6 years, and 22% of participants were men (Table 1). Twenty-one percent had diabetes, and 64% had hypertension. During 10-year follow-up, 393 participants (17.5%) died from all causes. In the validation cohort, the mean age of the participants was 63.8 ± 2.6 years, and 42% were men. Twenty-four percent had diabetes, and 47% had hypertension. During 10-year follow-up, 60 participants (8.7%) died from all causes.

Multivariable Results

We used Cox proportional hazards regression models to build the 10-year mortality risk prediction model, yielding C-statistics of 0.73, and ROC area of 0.74 in the development cohort (Table 2A). Additionally, we categorized the continuous variables in the regression model to create a point scoring system, which had comparable C-statistic and AUC to that of model 1 (Table 2B). Age over 80 years was the most powerful predictor of mortality, and male sex, smoking, diabetes, high blood pressure and WBC, and low total cholesterol and hemoglobin were significant risk factors for mortality. We also used the NRI-driven forward variable selection to verify whether this method yielded the similar results. The model building stopped at step 9 as no additional statistically significant values of NRI were observed (Supplementary Table 1, http://links.lww.com/MD/A674). In the final model, the same variables were selected as shown in Table 2, and the associated C-statistic was 0.73. The calibration of the model was good, with close agreement between the observed and predicted risk (Supplementary Figure 1, http://links.lww.com/MD/A674).

Point Scoring System

For each risk factor, points were calculated based on the estimate. Adding up these points yielded the total risk score, which corresponds to the mortality risk for each participant (Table 3). Risk score ranged from 0 to 20 points in the development cohort and 0 to 12 points in the validation cohort. Subjects were divided into 4 groups according to risk score (Table 4). In the development cohort, 10-year mortality was 6.6% in the lowest-risk group (0∼4 points), and was 38.4% in the highest-risk group (≥10 points). In the validation cohort, 10-year risk was comparable with the development cohort in the lowest- to intermediate-risk groups (ranged from 5.2% to 16%). However, in the highest-risk group, the observed mortality in the validation cohort was lower than in the development cohort, owing to the limited number of subjects with high risk. The C-statistic of the model was slightly higher in the development cohort than in the validation cohort (0.73 vs 0.67).

DISCUSSION

The aging of a population rapidly increases the burden on a health care system and attracts the attention of health care professionals and policy makers around the world. The present

TABLE 2. Multivariate HRs with 95% CIs for 10-year Risk of Death in the Development Cohort (A) Model 1 (B) Model 2

	Estimates	SE	*P*	HR	95% CI	
Age	0.107	0.008	<0.0001	1.113	1.095	1.131
Male	0.608	0.135	<0.0001	1.837	1.409	2.394
Smoking	0.726	0.136	<0.0001	2.068	1.583	2.700
SBP	0.006	0.002	0.013	1.006	1.001	1.010
FPG	0.006	0.002	<0.001	1.006	1.003	1.009
Log (TG)	0.270	0.116	0.020	1.310	1.044	1.644
TC	−0.006	0.002	0.001	0.994	0.991	0.998
WBC	0.029	0.013	0.030	1.029	1.003	1.056
HB	−0.111	0.040	0.006	0.895	0.827	0.969
C-statistic (95% CI)	0.728 (0.703–0.753)					
AUC (95% CI)	0.744 (0.717–0.771)					
Age, y						
<70	*Ref*					
70–79	1.037	0.119	<0.0001	2.820	2.234	3.560
≥80	1.929	0.167	<0.0001	6.885	4.960	9.555
Sex						
Male	0.526	0.121	<0.0001	1.693	1.336	2.144
Female	*Ref*					
Smoking						
No	*Ref*					
Yes	0.683	0.136	<0.0001	1.980	1.517	2.584
SBP, mmHg						
<160	*Ref*					
≥160	0.265	0.113	0.0188	1.303	1.045	1.626
Diabetes						
No	*Ref*					
Yes	0.421	0.114	0.0002	1.524	1.218	1.907
TG, mg/dL						
<200	*Ref*					
≥200	0.203	0.129	0.1173	1.224	0.950	1.578
TC, mg/dL						
<200	0.250	0.107	0.0194	1.284	1.041	1.584
≥200	*Ref*					
WBC						
<7	*Ref*					
≥7	0.328	0.112	0.0034	1.388	1.115	1.728
Hb, g/dL						
<12	0.375	0.149	0.0118	1.455	1.087	1.949
≥12	*Ref*					
C-statistic (95% CI)	0.734 (0.710–0.758)					
AUC (95% CI)	0.746 (0.720–0.772)					

AUC = area under the curve, CI = confidence interval, FPG = fasting plasma glucose, Hb = hemoglobin, SBP = systolic blood pressure, SE = standard error, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count (count/uL).

study provides a novel prognostic index estimating long-term mortality in community settings. This index can assist in clinical decision-making and may serve as an important tool to assess the impact of complex health status on mortality among elderly Asian population. Our index demonstrated strong discrimination among individuals, which was shown by increasing risk of mortality by point score, as well as good calibration in the low- to intermediate-risk categories.

Risk prediction is essential for therapeutic intervention to lower the likelihood of an unfavorable health outcome. In particular, clinical decisions are often influenced by either very low or very high mortality risk. Because the benefits of cancer screening are not evident until after 5 years, recent cancer screening guidelines recommend targeting screening for individuals with a life expectancy of >5 years.[2,3,6] Our index may be practical in identifying low-risk elderly individuals who may benefit from cancer screening. Furthermore, our index may be useful to determine individualized targets for cardiometabolic risk factors, such as blood pressure and glucose levels, to balance the benefits and risks of intensive control. Finally, epidemiological and clinical studies may use our index to examine the impact of exposure or treatment on mortality, as well as risk adjustment.

Although several indices have been developed to discriminate between high- and low-risk elderly groups, most previous studies used white populations for the development of a

TABLE 3. Calculation of Point Scoring for 10-year Mortality Index Point Scoring for 10-year Mortality Index

Step		Points	Point Total	Risk (%)
1	Age, y		0	4.8
	<70	0	1	5.8
	70–79	5	2	7.1
	≥80	10	3	8.6
2	Sex		4	10.4
	Male	3	5	12.6
	Female	0	6	15.2
3	Smoking		7	18.3
	No	0	8	21.9
	Yes	3	9	26.1
4	SBP, mmHg		10	30.9
	<160	0	11	36.4
	≥160	1	12	42.6
5	Diabetes		13	49.3
	No	0	14	56.5
	Yes	2	15	63.9
6	TG, mg/dL		16	71.3
	<200	0	17	78.3
	≥200	1	18	84.6
7	TC, mg/dL		19	89.9
	<200	1	20	93.9
	≥200	0	21	96.8
8	WBC		22	98.5
	<7	0	23	99.4
	≥7	2	24	99.8
9	Hb, g/dL		25	100.0
	<12	2		
	≥12	0		

Hb = hemoglobin, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count (count/uL).

mortality risk score. Lee et al[18] developed and validated a prognostic index for 4-year mortality among men and women aged 50 and older. In that study of community-dwelling US adults, they used 2 demographic variables (age and sex), 6 comorbid conditions (diabetes, cancer, lung disease, heart failure, current tobacco use, and body mass index [BMI] <25 kg/m^2), and 4 functional variables (bathing, walking several blocks, managing money, and pushing large objects).[18] Mazzaglia et al[19] produced prognostic indexes for short-term (15-month) mortality among community-dwelling Italian individuals aged 65 years and older. Based upon a 7-item questionnaire, the mortality rate ranged from 0.8% in the lowest risk group to 9.4% in the highest risk group.[19] The High-Risk Diagnoses for the Elderly Scale, using information from administrative data, showed a C-statistic of 0.68 in a model that includes 10 different comorbidities.[20] Carey et al[21] developed a multidimensional prognostic index using 8 independent risk factors, including age, sex, functional status, and comorbid conditions, to estimate 1- and 3-year mortality. Their index showed relatively good discrimination, with AUCs for mortality of 0.66.[21] To develop an index to predict 5-year mortality among community-dwelling older individuals, Schonberg et al[22] used 39 risk factors, including demographic, behavior, illness, and functional measures. The algorithm to predict 10-year mortality risk demonstrated that living area, older age, male sex, no high school completion, smoking, SBP ≥160 mmHg, low-density lipoprotein cholesterol ≥200 mg/dL, and diabetes were independent determinants in a general French population aged 35 to 64 years.[23] In Asia, most previous studies were performed using analyses of specific risk factors or of patients with a specific disease. Yang et al[24] reported an all-cause mortality risk score among patients with type 2 diabetes mellitus in Hong Kong. They found that age, sex, peripheral artery disease, cancer history, insulin use, blood hemoglobin levels, linear-transformed BMI, random spot urinary albumin-creatinine ratio, and estimated glomerular filtration rate at enrollment were significant predictors of mortality.[24] Recently, body size shape and fitness are reported to be important risk factors for mortality especially in elderly. A body shape index showed a stronger association with total, CVD, and cancer mortality compared with other anthropometric measures in elderly men.[25] Furthermore, in the Cooper Center Longitudinal Study, physical fitness in addition to the traditional risk factors predicted the 30-year risk for CVD mortality with C-statistics of 0.81 and 0.86 for both men and women.[26]

TABLE 4. Ten-year Mortality Rates by Risk Score Categories in the Development and Validation Cohorts

	Development			Validation		
	Deaths	N	Mortality (%)	Deaths	N	Mortality (%)
0–4 Points	55	832	6.6	20	381	5.2
5–7 Points	88	594	14.8	23	192	12.0
8–9 Points	58	318	18.2	13	81	16.0
≥10 Points	192	500	38.4	4	25	16.0

In this study, although we did not include the measures for fitness or sarcopenia, the predictive mortality index incorporates easily available demographic and laboratory variables, such as age, sex, smoking, lipid profiles, blood pressure, fasting glucose, white blood cells, and hemoglobin. To minimize subjective estimation and decrease dependence on a physician or patient's memory, we attempted to develop as simple of an index as possible using objective variables. Our index discrimination with a C-statistic of 0.73 shows favorable comparison with other widely used prognostic indexes, such as the Framingham (0.77–0.74) for prediction of CHD[27] and the Charlson-Deyo for prediction of mortality among patients with comorbid conditions (0.60–0.78).[28] The algorithm to predict 10-year risk of all-cause mortality used 8 risk factors and showed a similar C-statistic of 0.76 based on a French MONICA study.[23]

The standardized data in our index can even be obtained retrospectively using routine health examination and medical record information. Increased mortality risk among elderly individuals is primarily explained by the influence of age itself, but may also be associated with prolonged exposure to risk factors. Sex is a critical variable in the estimation of mortality; usually females are at a lesser risk than males. Anemia is now recognized to be a mortality multiplier among diabetic and nondiabetic subjects.[29] Venskutonyte et al[30] developed a cardiometabolic risk index based on HDL-C and fasting plasma glucose in an elderly Swedish population. They found HDL-C to be a relatively stable variable for predicting mortality in both sexes. In the present study, the incorporation with HDL-C into the model did not significantly increase the predictability or C-statistics. However, fasting plasma glucose levels were adopted in both indices for prediction of mortality in elderly European

and Asian populations. Previous studies have shown FPG to be a strong predictor of mortality in both sexes and a strong predictor of cardiovascular risk among women.[31–33] Our study is in agreement with results that emphasize the assessment of metabolic syndrome and their clustering among elderly adults as important markers of an increased risk for mortality among both white and Asian individuals.[34,35]

The present study has its own strengths. In the development cohort, the uniform age, the recruitment of subjects without severe disease from community-dwelling population, and the long period of follow-up with a high mortality may be considered strengths. Furthermore, this is a unique predictive mortality index, which was developed and validated by 2 independent longitudinal cohorts, all Asian elderly adults. We observed good agreement between 10-year mortality in our 2 independent cohorts, especially in the low- to intermediate-risk groups.

There are several limitations in our study. First, since our index focused on community-dwelling elderly individuals, this index might not be applicable to institutional populations or patients with specific severe diseases. Second, certain predictors, such as cognitive status or functional variables, were not available in this study, and may increase prediction among elderly adults. Finally, the younger age of the validation cohort relative to the development cohort makes it difficult to compare the mortality among high-risk participants.

In conclusion, our predictive mortality index with a simple additive point system may be a potentially practical tool for use in community settings and can estimate prognosis for long-term mortality to assist in the decision-making of clinicians, researchers, and policy makers. To be a generally useful tool, it may be better that this finding should be confirmed in other elderly populations.

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