

SCIENTIFIC REPORTS

OPEN

Prediction of mortality in Chinese very old people through the frailty index based on routine laboratory data

Qiukui Hao¹, Xuelian Sun¹, Ming Yang¹, Biao Dong^{1,2}, Birong Dong¹ & Yuquan Wei²

The increased risk of death in older adults can be successfully identified through frailty index (FI), based on comprehensive geriatric assessment data and self-reported data from the accumulated deficit, although the method depending on routine laboratory data (FI-LAB) remains uncertain. In the current study, the capacity of FI-LAB in evaluating the risk of mortality in a very old Chinese community cohort was analyzed. The 90-year- and above old individuals from a Dujiangyan community in Sichuan Province, China, who had completed a health assessment at baseline (in 2005) and whose laboratory data were analyzed ($n = 736$) from cumulative data from the Project of Longevity and Aging. The FI-LAB data was constructed from routine laboratory data and calculated as the ratio of abnormal factors in 22 variables (including red blood cells, white blood cells, and alanine transaminase) that can be assessed through blood tests. The multivariable Cox regression was used to evaluate the effect of frailty on death. In the four-year follow-up, 53.5% of the 736 participants (age = 93.6 ± 3.4 years; 67.5% women), were reported dead. The FI-LAB mean baseline value was 0.21 (standard deviation = 0.10; range = 0 to 0.55). Frailty (after adjusting for gender, age, and other confounders) could be directly correlated with increased death risk, with a hazard ratio of 1.31 (95% confidence interval (CI): 1.07–1.61) in comparison with those without frailty among the individuals. Frailty as defined by FI-LAB, established only on routine laboratory data, indicates a significant death risk in the very old people.

A familiar geriatric syndrome, called frailty represents a state in which the body's physiological reserves decrease and vulnerability to stressor events increases¹. The prevalence of frailty varies from 4.0% to 59.1% in community-dwelling adults aged 65 and above². Adverse outcomes, including falls, delirium, and disability are much more likely in frail older people. As such, frailty is an emerging health priority^{1,3}. Identifying frailty in older people is very important, but its diagnostic criteria are still widely debated⁴. More than 10 diagnostic assessment tools for frailty are currently available⁵, amongst which the frailty index based on cumulative health-related deficits, is one of the more commonly used methods^{1,5}.

For building an index of frailty for older people, the individuals' health-related deficits must be counted. The deficits must be chosen according to the following principles: pertaining to the health status; no early saturation; cover a range of systems; to compare the same people, the deficits that define the frailty index must be identical; the total number of deficits should be at least 30–40⁶. Typically, the deficits are symptoms, ailments, disabilities, and other measures^{6,7}. The cumulative number of deficits present in an older person, divided by the sum total of all the deficits under review is defined as the frailty index⁶. For instance, if 30 deficits are reviewed, and if an individual has three of these deficits, that frailty index would be 0.01 (3/30). Thus, the range of a frailty index is 0 to 1 with higher frailty index scores suggesting a greater frailty level⁸.

In hospitalized older people and community-dwelling, the frailty index appears to be a strong predictor of adverse clinical outcomes^{9,10} and provides a quantitative measure of frailty. However, the construction of a frailty index in a busy clinical setting is time-consuming. This can be circumvented by building a frailty index that depends on routinely collected clinical data. In a Canadian Study of Health and Aging (CSHA) cohort,

¹The Center of Gerontology and Geriatrics/National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China. ²Key Laboratory of Biotherapy and Cancer Center/Collaborative Innovation Center for Biotherapy, West China Hospital, Sichuan University, Chengdu, China. Correspondence and requests for materials should be addressed to Birong Dong (email: birongdong@163.com)

Howlett and colleagues reviewed 21 laboratory variables and constructed a frailty index (FI-LAB). They found that FI-LAB could identify older adults with an increased death risk (hazard ratios 1.03; 95% confidence interval: 1.02 to 1.04)¹¹. Several other studies reported that FI-LAB was feasible, valid, and closely associated with frailty indexes based on complex, self-reported data for the prediction of mortality^{12–14}. However, these studies only included 35 to 89 years old Caucasian individuals, with the mean age of 60 years. At the advanced stage of life, the association between abnormal lab variables and adverse outcomes may differ in relatively young old people. For example, at midlife, metabolic syndrome correlates with lower cognitive function although it shows an inverse association in those in an advanced stage of life^{15–17}. Also, our team found that the frailty index (based on geriatric assessment data without cognitive evaluation) may differ in predicting late-life mortality than in relatively younger adults¹⁸.

The role of FI-LAB in predicting mortality in advanced/late life has not been reported until now. As such, the relationship between FI-LAB and mortality has remained unclear regarding very old populations (90 years and above). From 2005 to 2009, we carried out a cross-sectional study on 870 adults of 90 years and above age, and obtained the mortality data in 2009. This study renders the opportunity to examine the role of FI-LAB in predicting mortality at an advanced stage of life.

Methods

The population under study. This study was carried out in 2005 in Dujiangyan, a town in South West China, as a part of the Project of Longevity and Aging in Dujiangyan (PLAD). In this cross-sectional study, 1115 community members who were aged 90 years and above were included, which was conducted to investigate the relationships amongst longevity, ailments that are age-related, lifestyle, environment, and other aspects. The PLAD methods have been previously described in earlier studies^{19–21}. Briefly, baseline data of 870 community members who consented to participate in the study, were collected through direct interviews. Trained medical staff carried out the physical examinations, measurements of body parameters, and fasting blood samples for all the individuals who participated. Formal informed consent was obtained from all participants or their legal representatives after the study details were explained to them. The Sichuan University's Research Ethics Committee (No. 20100325) approved the study protocols. Relevant guidelines and regulations were followed while performing all the methods. For this analysis, participants lacking mortality data (53 cases) or blood samples (81 cases) were excluded, resulting in a study sample of 736 (males: 239; females: 497).

Construction of the frailty index based on lab variables. The frailty index did not rely on a specific variable⁶. The FI-LAB was first validated using 21 laboratory variables in addition to systolic and diastolic blood pressure in the CSHA study¹¹. The FI-LAB typically requires 20 or more variables, at least 70% of which are considered lab variables for a given individual¹¹. Studies validating FI-LAB has been successfully replicated in many groups of elderly individuals^{12,13}. In this study, we constructed a frailty index based on 22 lab variables, which were parameters for a fasting blood sample. Variables were selected according to previous studies¹¹ and available items in the PLAD study. All considered variables included counts of white blood cells, neutrophilic leukocytes, platelets, hematocrit, red blood cells, hemoglobin, the mean values of corpuscular volume, cell hemoglobin, and corpuscular hemoglobin concentrations (MCV, MCH, and MCHC, respectively), blood glucose, total and direct bilirubin (TBil and DBil, respectively), alanine transaminase (ALT), albumin (Alb), globulin (Glob), urea, creatinine (CREA), uric acid (URIC), cholesterol (CHOL), high-density and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively), and triglycerides (TG). Each variable was coded as either 1 or 0, with 1 indicating that the values exceeded the normal range or cut-offs (deficits), and 0 indicating that the values were within the normal range (Table 1)²². Here, the sum of all existing parameter deficits, divided by the total of all the considered parameters (here, 22) defined the FI-LAB. Theoretically, the FI-LAB is an uninterrupted score between 0 to 1 for each given individual. In this study, established FI-LAB cut-points (0.21) were employed according to the previous study conducted by Hoover and colleagues²².

The data for mortality and other co-variables. We collected mortality data in 2009 for all participants excluding 48 individuals (5.5%) from relatives, or neighbors and local government records. The status of the patient: survived, or dead, and the time of death was recorded. We also collected the following information as co-variables: individual's education (illiterate, primary, secondary, and advanced level), age, gender, and chronic disease using a general questionnaire in the PLAD study through direct interviews by volunteers who were appropriately trained. All the reported chronic ailments were diagnosed by local certified physicians.

Statistical analysis. To explain the baseline characteristics, descriptive statistics were used. The continuous or categorical variables were described using mean values, standard deviation (SD), numbers or percentages. For continuous and categorical variables, the differences between survival and frailty status (determined by FI-LAB) were evaluated by applying the unpaired Student's *t*-test and the chi-square test, respectively. We applied regression models of Cox proportional hazard to determine the hazard ratio (HR) and its 95% confidence intervals (CI) of frailty, with a function of increased mortality represented by each parameter in FI-LAB and overall frailty status. The general covariates like gender, age, and educational levels were calibrated in an adjusted Cox regression model. We also further adjusted for other aspects of lifestyle like the smoking habit, alcohol intake, exercise, and chronic ailments such as confounding factors in the Cox regression model. The SPSS version 17.0 for Windows software package, (SPSS Inc., Chicago, IL, USA) were applied for all statistical analyses and plots. The statistically significant values were set as two-tailed *P* at <0.05.

	Frailty		P value
	No (n = 364)	Yes (n = 372)	
Age (years)	93.7 ± 3.4	93.5 ± 3.4	0.418
Female (%)	75.8	59.4	<0.001**
BMI (kg/m ²)	19.5 ± 3.2	19.1 ± 3.7	0.087
Weight (kg)	41.2 ± 8.1	41.4 ± 8.9	0.697
Height (cm)	145.4 ± 9.7	147.6 ± 10.2	0.003**
WC (cm)	77.1 ± 9.7	77.1 ± 9.1	0.945
SBP (mmHg)	141.4 ± 22.8	138.8 ± 23.1	0.128
DBP (mmHg)	73.4 ± 12.6	72.3 ± 11.6	0.233
Education level (%)			
Illiteracy	76.9	67.9	
Primary school	20.4	29.9	
Secondary school or advanced	2.8	2.2	0.012*
Smoking (%)	39.8	47.0	0.049
Alcohol drinking (%)	26.6	25.1	0.637
Having exercise habit (%)	40.2	37.0	0.379
TG (mmol/l)	1.2 ± 0.7	1.2 ± 0.7	0.804
TC (mmol/l)	4.3 ± 0.7	4.0 ± 0.9	<0.001**
HDL-C (mmol/l)	1.6 ± 0.5	1.5 ± 0.7	0.180
LDL-C (mmol/l)	2.3 ± 0.6	2.2 ± 0.6	0.017*
SUA (μmol/l)	311.1 ± 74.9	328.7 ± 97.8	0.006**
Hypertension	9.6	10.5	0.695
Cardiovascular disease	4.9	4.6	0.811
Cerebrovascular disease	2.7	1.3	0.187
Diabetes	1.4	0.5	0.282
Respiratory disease	17.6	12.9	0.077
Digestive disease	16.8	17.7	0.724
Chronic renal disease	2.5	2.4	0.963
Osteoarthritis	28.8	29.8	0.767
Status of survival			
Surviving (%)	50.8	42.2	
Death (%)	49.2	57.8	0.019*

Table 1. Characteristics of the study population according to frailty assessed by FI-LAB. Data are the mean ± SD unless otherwise indicated. *P < 0.05, **P < 0.01. Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

Results

The study samples and frailty. In total, 736 participants, whose age ranged from 90 to 108 and mean age of 93.6 ± 3.4 years, were included. The percentage of females was 67.5%. The participants' median, FI-LAB, and maximum mean scores were 0.23, 0.55, and 0.21, respectively, with a standard deviation of 0.10. The FI-Lab-99th percentile score was 0.48. The overall prevalence of frailty was 50.5% (FI-LAB ≥ 0.21; 95% CI = 46.9–54.1%). Men had significantly higher FI scores compared to that of women (0.24 ± 0.10 vs. 0.20 ± 0.10; t = 5.32, p < 0.001), and the frailty group had more men than women (63.2% vs. 44.5%, respectively, X² = 22.6, p < 0.001). Subjects with frailty had significantly lower educational levels, total cholesterol (TC), and LDL-C levels but significantly higher height and serum uric acid levels. The control group had a higher proportion of exercise habit than the frailty group. Table 1 presents the attributes of subjects having or lacking frailty.

The study sample and mortality. The sample had 53.5% rate of 4-year mortality rate. The subjects who were dead were slightly older and frailer than those in the survival group (93.9 ± 3.4 vs. 93.3 ± 3.4, t = 2.23, p = 0.026; 0.22 ± 0.1 vs. 0.20 ± 0.1, t = 2.79, p = 0.005). The death group had a higher proportion of frailty compared to that of the survival group (36.8% vs. 29.2%, respectively, X² = 4.72, p = 0.030). The survival group had a higher proportion of exercise habit than the death group (45.9% vs. 32.2%, respectively, X² = 4.72, p < 0.001). The survival group had less incidences of respiratory disease than those in the death group (12.3% vs. 17.8%, X² = 4.27, p = 0.039). Table 2 shows the attributes of subjects according to the status of survival.

The frailty and mortality correlation. Statistical analysis of most variables (neutrophilic leukocytes, platelets, red blood cells, MCV, MCH, MCHC, blood glucose, TBil, DBil, ALT, Alb, Glob, CREA, URIC, CHOL,

	Status of survival		P value
	Alive (n = 342)	Death (n = 394)	
Age (years)	93.3 ± 3.4	93.9 ± 3.4	0.026*
Female (%)	69.0	66.2	0.425
BMI (kg/m ²)	19.4 ± 3.3	19.2 ± 3.6	0.374
Weight (kg)	41.3 ± 8.1	41.2 ± 8.8	0.890
Height (cm)	146.5 ± 10.0	146.5 ± 10.0	0.940
WC (cm)	76.8 ± 9.5	77.3 ± 9.3	0.504
SBP (mmHg)	140.1 ± 22.3	140.2 ± 23.6	0.935
DBP (mmHg)	72.2 ± 11.4	73.4 ± 12.7	0.155
Education level (%)			
Illiteracy	72.4	72.3	
Primary school	25.2	25.2	
Secondary school or advanced	2.3	2.5	0.985
Smoking (%)	45.6	41.6	0.272
Alcohol drinking (%)	27.3	24.6	0.402
Having exercise habit (%)	45.9	32.2	<0.001**
Frailty (%)	29.2	36.8	0.030*
TG (mmol/l)	1.2 ± 0.7	1.2 ± 0.7	0.765
TC (mmol/l)	4.2 ± 0.8	4.1 ± 0.8	0.351
HDL-C (mmol/l)	1.6 ± 0.6	1.6 ± 0.7	0.616
LDL-C (mmol/l)	2.3 ± 0.6	2.3 ± 0.6	0.981
SUA (μmol/l)	318.3 ± 86.8	321.5 ± 88.4	0.617
Hypertension	8.8	11.2	0.281
Cardiovascular disease	5.0	4.6	0.798
Cerebrovascular disease	2.6	1.5	0.288
Diabetes	0.3	1.5	0.130
Respiratory disease	12.3	17.8	0.039*
Digestive disease	16.1	18.3	0.432
Chronic renal disease	2.0	2.8	0.514
Osteoarthritis	26.6	31.7	0.128

Table 2. Characteristics of the study population according to status of survival. Data are the mean ± SD unless otherwise indicated. *P < 0.05, **P < 0.01. Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure, SD, standard deviation.

TG, HDL-C, and LDL-C) that comprised the FI-LAB did not increase the risk of four-year mortality. The hemoglobin (HR: 1.40, 95% CI: 1.05–1.86), white blood cell count (HR: 1.37, 95% CI: 1.12–1.69), and hematocrit (HR 1.26; 95% CI: 1.03–1.53) increased the risk of mortality. Table 3 shows the relationship between each selected variable in the FI-LAB and death. The outcomes from the adjusted and unadjusted Cox regression models of frailty and mortality are presented in Table 4. The frailty had a notably increased risk of mortality compared to the subjects without frailty, (HR: 1.32, 95% CI: 1.08–1.61). The model for Cox proportional hazard regression was quite stable (HR: 1.31, 95% CI: 1.07–1.61) after compensating for gender, age, alcohol intake, smoking, exercise, and several chronic ailments (hypertension, cardiovascular-, cerebrovascular-, respiratory- and digestive- diseases, osteoarthritis, chronic renal disease, and diabetes). The cumulative death hazard of the study population based on frailty at baseline is presented in Fig. 1.

Discussion

In this study, we investigated the correlation between mortality and FI-LAB in 90–108 years old individuals in Dujiangyan city, Sichuan Province, China, to gain an understanding of how frailty is assessed based on abnormal routine blood parameters that influence the risk of death at an advanced stage of life. We believe that this is the first study of its kind that evaluates the link between FI-LAB and mortality in a specific population. We show that frailty assessed through routine blood parameters is linked to an increased risk of mortality than those of the control group, which indicates that attention must be given to abnormal routine blood parameters even among very old people.

We also found that men were more prone to frailty than women, according to both FI-LAB scores and frailty prevalence. This differed from previous studies employing the Fried phenotype and frailty index defined on the basis of comprehensive geriatric assessment^{2,23–25}. The majority of studies found that females had a greater frailty

Standard laboratory variables	Normal range or cutoff	HR (95% CI) for 4-year mortality	P-value
White blood cells (number/L)	Men 4.0–9.2, women 3.7–9.2	1.40 (1.05–1.86)	0.021*
Neutrophil (%)	50–70	1.18 (0.94–1.48)	0.153
PLT (number/L)	100–300	1.02 (0.84–1.25)	0.822
Red blood cells (number/L)	Men 4.1–5.7 women 3.7–5.1	1.19 (0.98–1.46)	0.079
HGB	Men 131–172 women 113–151	1.37 (1.12–1.69)	0.007**
HCT	Men 0.38–0.51 women 0.34–0.45	1.26 (1.03–1.53)	0.023*
MCV	Men 83.9–99.1 women 32.6–99.1	1.01 (0.71–1.45)	0.948
MCH	Men 27.8–33.8 women 26.9–33.3	1.21 (0.92–1.58)	0.168
MCHC	Men 320–355 women 322–362	1.25 (0.98–1.58)	0.074
Blood sugar (mmol/L)	3.9–6.1	0.93 (0.76–1.13)	0.438
TC	<5.18	0.87 (0.63–1.21)	0.399
TG	<1.70	0.97 (0.72–1.29)	0.814
LDL-C	<3.37	1.15 (0.74–1.77)	0.524
HDL-C	≥1.04	0.91 (0.53–1.55)	0.720
TBIL	3.4–17.1	0.85 (0.62–1.16)	0.305
DBIL	<3.4	1.13 (0.91–1.40)	0.262
ALT	<55	0.05 (0.01–4.52)	0.191
Alb	35–55	1.54 (0.73–3.25)	0.258
Glob	9–34	1.03 (0.70–1.54)	0.868
BUN	2.9–8.2	1.14 (0.89–1.47)	0.295
Creatinine	53–140	1.24 (0.84–1.83)	0.289
SUA (μmol/l)	240–490	1.16 (0.91–1.48)	0.225

Table 3. Routine blood laboratory variables used to construct the FI-LAB. Abbreviations: HR, hazard risk; CI, confidence interval; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TBil, total bilirubin; DBil, direct bilirubin; ALT, alanine transaminase; Alb, albumin; Glob, globulin; BUN, blood urea nitrogen; SUA, serum uric acid. *P < 0.05, **P < 0.01.

	No frailty	Frailty HR (95% CI)
Unadjusted model	1 (Reference)	1.32 (1.08, 1.61)
Adjusted model 1 ^a	1 (Reference)	1.33 (1.09, 1.63)
Adjusted model 2 ^b	1 (Reference)	1.31 (1.07, 1.61)
Adjusted model 3 ^c	1 (Reference)	1.31 (1.07, 1.61)

Table 4. Estimate of the accuracy of the FI-LAB on mortality, modeled with Cox regression. ^aAdjusted for age, gender, educational levels. ^bAdjusted for age, gender, educational levels, smoking, alcohol drinking, exercise habit. ^cAdjusted for age, gender, educational levels, smoking, alcohol drinking, exercise habit, hypertension, cardiovascular disease, cerebrovascular disease, diabetes, respiratory disease, digestive disease, chronic renal disease, and osteoarthritis. Abbreviations: HR, hazard risk; CI, confidence interval. *P < 0.05, **P < 0.01.

burden than males, even though females usually live longer than men²⁶. One reason for this phenomenon was that the frailty phenotype and frailty index are based on comprehensive geriatric assessments, which may not include all variables that affect life expectancy in older people²⁶. One previous study that employed laboratory parameters to compile the frailty index also found that men had higher FI-LAB scores than women among older inpatients¹⁴. The study, however, included only 306 inpatients with an average age of 82.9 ± 6.4 years, with the mean FI-LAB scores of 0.34 ± 0.15, which was higher than the FI-LAB score in our sample (0.21 ± 0.10). The main reason for these differences is that older people who require hospitalization are typically frailer than those from the community. Laboratory variables were also more objective than health-related deficits from self-reported data²⁷. This indicated that the FI-LAB can capture other factors that influence mortality to a higher level than other frailty assessment methods, particularly amongst old men.

Several studies have reported that the FI-LAB can predict mortality, and yielded results similar to this study. However, these studies included participants with ages ranging from 35 to 89 years old^{11–14}. One of the studies found that the association of FI-LAB and mortality was not statistically significant amongst those aged 20–39 years old¹². Thus, the role of FI-LAB in predicting death differed amongst age groups and the relationship between FI-LAB and mortality was indefinable in very old people. This, therefore, extends previous conclusions to a group with very old individuals.

Interestingly, we found that the majority of variables that made up the FI-LAB did not elevate the four-year mortality risk, except hemoglobin (HR: 1.40, 95% CI: 1.05–1.86), white blood cell count (HR: 1.37, 95% CI:

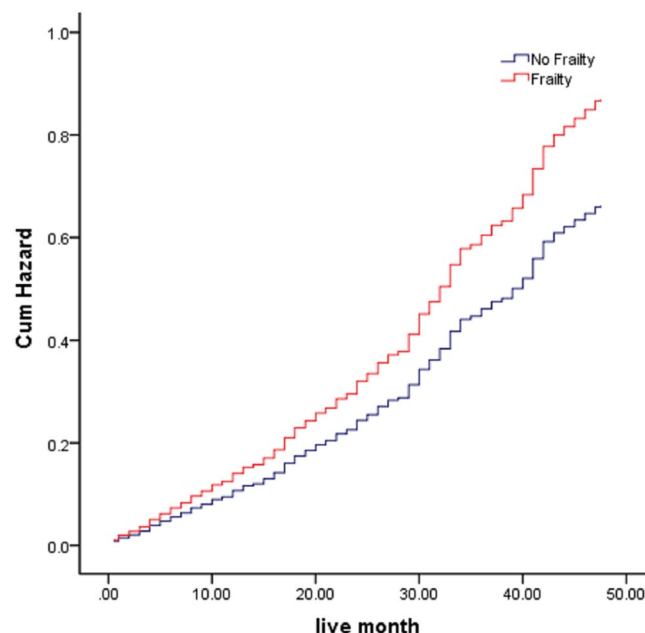


Figure 1. Cumulative hazard of death in the study population, according to frailty at baseline.

1.12–1.69), and hematocrit (HR: 1.26, 95% CI: 1.03–1.53). After excluding these variables (hemoglobin, white blood cell count, and hematocrit), we also found that an FI-LAB score (based on 19 other variables) divided by 0.25 or 0.21, could show a higher risk of mortality in Cox regression models (HR: 1.26, 95% CI: 1.01–1.57; HR: 1.17, 95% CI: 0.96–1.42, respectively). These results are in accordance with the theory of health-related deficits accumulation, developed by Rockwood and colleagues, and the accumulation of subclinical deficits was demonstrated by FI-LAB^{12,28}. In clinical practice, we must also be aware of the accumulation of these abnormal variables in the laboratory parameters.

In a four-year retrospective cohort study, Cheung and colleagues included 266 patients with trauma (mean age 76.5 ± 7.8 years), collected samples within 48 hours of presentation at the hospital and constructed an FI-LAB using 23 parameters²⁹. The study found that frailty on admission, as defined by an FI-LAB > 0.4 , was not associated with discharge destination, in-hospital complications, and other adverse outcomes. To our knowledge, no previous studies have focused on the correlation between FI-LAB and disease prognosis in older people. Whether FI-LAB can be used for clinical decisions should be further investigated.

Numerous studies have found that low levels of education are a risk factor of frailty and associated physical and cognitive function in older people^{25,30–32}. While education is not directly involved in the pathophysiology of frailty, it can benefit an individual's health by selecting a health-related lifestyle. However, the evidence regarding the protective effects of higher education in frailty amongst very old individuals was scarce. In this study, we indicated that the education found amongst nonagenarians or centenarians had protective effects. Consistent with previous studies, We also found that the risk of frailty is directly associated with exercise³³. Moreover, the guideline of frailty management in older people also recommends exercise³⁴. Concomitantly, this study supports the idea that older individuals should maintain exercise at advanced stages of life. However, we did not adjust potential variables and bias in the results may therefore exist.

Nevertheless, the study had a few limitations, so, data in this study must be explained with caution. Firstly, the number of subjects was smaller ($n = 736$) than the cohort studies from Canada. In addition, the subgroup analysis based on frailty at different levels was limited due to the small number of participants. However, this remains the first study to explore the role of FI-LAB in predicting mortality among very old individuals, and it is difficult to collect data in this age group. Secondly, we only included nonagenarians or centenarians (Han Chinese) which may cause survival bias, which is obvious while studying the individuals of this very old group. Thus, we cannot extend the present findings to general old people and other races in general. Thirdly, other potential confounders, including income and a family history of chronic disease were not adjusted for. The majority (90%) of participants were farmers and lived in rural areas. Many differences in the characteristics of frailty between rural and urban populations in Chinese elderly people exist³⁵. Therefore, the urban population may not have been effectively represented by the participants in this study. Fourthly, this study did not provide data involving grip strength and speed of walking, which was part of the Project of Longevity and Aging in Dujiangyan, thus, the role of frailty defined as the frailty phenotype could not be explored. However, the frailty-phenotype and -index are comparable, particularly when the cut-off point of a frailty index is set at 0.20–0.25^{22,36}. Furthermore, recent studies found that both the frailty index and frailty phenotype can predict the three-year mortality risk, even though the discrimination of frailty gradually declines with increasing age³⁷.

Conclusions

Frailty, as evaluated by routine blood parameters is linked with a higher risk of mortality. This indicates that more attention should be paid to abnormal routine blood parameters amongst very old individuals when the death risk at advanced stages of life is assessed.

References

- Clegg, A., Young, J., Iliffe, S., Rikkert, M. O. & Rockwood, K. Frailty in elderly people. *Lancet* **381**, 752–762, [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9) (2013).
- Collard, R. M., Boter, H., Schoevers, R. A. & Oude Voshaar, R. C. Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society* **60**, 1487–1492, <https://doi.org/10.1111/j.1532-5415.2012.04054.x> (2012).
- Cesari, M. *et al.* Frailty: An Emerging Public Health Priority. *Journal of the American Medical Directors Association* **17**, 188–192, <https://doi.org/10.1016/j.jamda.2015.12.016> (2016).
- Rodriguez-Manas, L. *et al.* Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *The journals of gerontology. Series A, Biological sciences and medical sciences* **68**, 62–67, <https://doi.org/10.1093/gerona/gls119> (2013).
- Dent, E., Kowal, P. & Hoogendijk, E. O. Frailty measurement in research and clinical practice: A review. *European journal of internal medicine* **31**, 3–10, <https://doi.org/10.1016/j.ejim.2016.03.007> (2016).
- Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M. & Rockwood, K. A standard procedure for creating a frailty index. *BMC geriatrics* **8**, 24, <https://doi.org/10.1186/1471-2318-8-24> (2008).
- Jones, D., Song, X., Mitnitski, A. & Rockwood, K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. *Aging Clin Exp Res* **17**, 465–471 (2005).
- Mitnitski, A. B., Mogilner, A. J. & Rockwood, K. Accumulation of deficits as a proxy measure of aging. *TheScientificWorldJournal* **1**, 323–336, <https://doi.org/10.1100/tsw.2001.58> (2001).
- Pena, F. G. *et al.* Comparison of alternate scoring of variables on the performance of the frailty index. *BMC geriatrics* **14**, 25, <https://doi.org/10.1186/1471-2318-14-25> (2014).
- Evans, S. J., Sayers, M., Mitnitski, A. & Rockwood, K. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. *Age Ageing* **43**, 127–132, <https://doi.org/10.1093/ageing/aft156> (2014).
- Howlett, S. E., Rockwood, M. R., Mitnitski, A. & Rockwood, K. Standard laboratory tests to identify older adults at increased risk of death. *BMC medicine* **12**, 171, <https://doi.org/10.1186/s12916-014-0171-9> (2014).
- Blodgett, J. M., Theou, O., Howlett, S. E. & Rockwood, K. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *Geroscience*, <https://doi.org/10.1007/s11357-017-9993-7> (2017).
- Rockwood, K., McMillan, M., Mitnitski, A. & Howlett, S. E. A Frailty Index Based on Common Laboratory Tests in Comparison With a Clinical Frailty Index for Older Adults in Long-Term Care Facilities. *Journal of the American Medical Directors Association* **16**, 842–847, <https://doi.org/10.1016/j.jamda.2015.03.027> (2015).
- Ritt, M., Jager, J., Ritt, J. I., Sieber, C. C. & Gassmann, K. G. Operationalizing a frailty index using routine blood and urine tests. *Clinical interventions in aging* **12**, 1029–1040, <https://doi.org/10.2147/cia.s131987> (2017).
- Luo, L., Yang, M., Hao, Q., Yue, J. & Dong, B. Cross-sectional study examining the association between metabolic syndrome and cognitive function among the oldest old. *Journal of the American Medical Directors Association* **14**, 105–108, <https://doi.org/10.1016/j.jamda.2012.10.001> (2013).
- van den Berg, E., Biessels, G. J., de Craen, A. J., Gussekloo, J. & Westendorp, R. G. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology* **69**, 979–985, <https://doi.org/10.1212/01.wnl.0000271381.30143.75> (2007).
- Launer, L. J. The epidemiologic study of dementia: a life-long quest? *Neurobiology of aging* **26**, 335–340, <https://doi.org/10.1016/j.neurobiolaging.2004.03.016> (2005).
- Hao, Q., Dong, B., Yang, M., Dong, B. & Wei, Y. Frailty and Cognitive Impairment in Predicting Mortality Among Oldest-Old People. *Front Aging Neurosci* **10**, 295, <https://doi.org/10.3389/fnagi.2018.00295> (2018).
- Wu, J. H. *et al.* Social functions of the longevous elderly population in Duijiangyan. *Sichuan Da Xue Xue Bao Yi Xue Ban* **38**, 484–487 (2007).
- Wang, Z. *et al.* Is there an association between mild cognitive impairment and dietary pattern in Chinese elderly? Results from a cross-sectional population study. *BMC Public Health* **10**, 595, <https://doi.org/10.1186/1471-2458-10-595> (2010).
- Flaherty, J. H. *et al.* Observational study of 1-year mortality rates before and after a major earthquake among Chinese nonagenarians. *The journals of gerontology. Series A, Biological sciences and medical sciences* **66**, 355–361, <https://doi.org/10.1093/gerona/gdq229> (2011).
- Hoover, M., Rotermann, M., Sanmartin, C. & Bernier, J. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. *Health Rep* **24**, 10–17 (2013).
- Chen, S. *et al.* Association between Angiotensin-converting enzyme insertion/deletion polymorphisms and frailty among chinese older people. *Journal of the American Medical Directors Association* **16**, 438 e431–436, <https://doi.org/10.1016/j.jamda.2015.01.094> (2015).
- Hao, Q., Song, X., Yang, M., Dong, B. & Rockwood, K. Understanding Risk in the Oldest Old: Frailty and the Metabolic Syndrome in a Chinese Community Sample Aged 90+ Years. *The journal of nutrition, health & aging* **20**, 82–88, <https://doi.org/10.1007/s12603-015-0553-5> (2016).
- Stanton, S. L., Seplaki, C. L., Thorpe, R. J., Jr, Allen, J. K. & Fried, L. P. Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. *Journal of epidemiology and community health* **64**, 63–67, <https://doi.org/10.1136/jech.2008.078428> (2010).
- Hubbard, R. E. & Rockwood, K. Frailty in older women. *Maturitas* **69**, 203–207, <https://doi.org/10.1016/j.maturitas.2011.04.006> (2011).
- Theou, O. *et al.* Measuring frailty using self-report and test-based health measures. *Age and ageing* **44**, 471–477, <https://doi.org/10.1093/ageing/afv010> (2015).
- Rockwood, K. Conceptual Models of Frailty: Accumulation of Deficits. *Can J Cardiol* **32**, 1046–1050, <https://doi.org/10.1016/j.cjca.2016.03.020> (2016).
- Cheung, A., Haas, B., Ringer, T. J., McFarlan, A. & Wong, C. L. Canadian Study of Health and Aging Clinical Frailty Scale: Does It Predict Adverse Outcomes among Geriatric Trauma Patients? *Journal of the American College of Surgeons* **225**, 658–665 e653, <https://doi.org/10.1016/j.jamcollsurg.2017.08.008> (2017).
- Mello Ade, C., Engstrom, E. M. & Alves, L. C. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. *Cadernos de saude publica* **30**, 1143–1168 (2014).
- Fransé, C. B. *et al.* Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PloS One* **12**, e0187946, <https://doi.org/10.1371/journal.pone.0187946> (2017).
- Tsai, Y. Education and disability trends of older Americans, 2000–2014. *J Public Health (Oxf)* **39**, 447–454, <https://doi.org/10.1093/pubmed/fdw082> (2017).

33. Tanimura, C. *et al.* Self-care agency, lifestyle, and physical condition predict future frailty in community-dwelling older people. *Nurs Health Sci*, <https://doi.org/10.1111/nhs.12376> (2017).
34. Dent, E. *et al.* The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty. *Journal of the American Medical Directors Association* **18**, 564–575, <https://doi.org/10.1016/j.jamda.2017.04.018> (2017).
35. Yu, P. *et al.* Frailty and survival of older Chinese adults in urban and rural areas: results from the Beijing Longitudinal Study of Aging. *Archives of gerontology and geriatrics* **54**, 3–8, <https://doi.org/10.1016/j.archger.2011.04.020> (2012).
36. Malmstrom, T. K., Miller, D. K. & Morley, J. E. A comparison of four frailty models. *Journal of the American Geriatrics Society* **62**, 721–726, <https://doi.org/10.1111/jgs.12735> (2014).
37. Kusumastuti, S., Gerds, T. A., Lund, R., Mortensen, E. L. & Westendorp, R. G. J. Discrimination ability of comorbidity, frailty, and subjective health to predict mortality in community-dwelling older people: Population based prospective cohort study. *European journal of internal medicine* **42**, 29–38, <https://doi.org/10.1016/j.ejim.2017.05.016> (2017).

Acknowledgements

We would like to thank the Department of Geriatrics staff at Dujiangyan Hospital, all participants and legal representatives for the contributions. This National Natural Science Foundation of China (No. 81601220), the Sichuan University's Science Foundation for Young Researchers of (2017SCU11044), and the Project of Science and Technology Bureau of China and Sichuan Province (2017RZ0040, 2017YFC0840101, and 2006Z09-006-4) collectively supported this study, but did not participate in any capacity in the study design, methods, data collection, analyses, or manuscript preparation.

Author Contributions

Qiukui Hao (Q.H.) conducted the data analysis and drafted the initial manuscript. Xuelian Sun (X.S.), Ming Yang (M.Y.) and Biao Dong (B.D.) help with results interpretation and give critical comments for the manuscript. Birong Dong (B.R.D.) and Yuquan Wei (Y.W.) secured funding for data collection and verified the analysis outcomes.

Additional Information

Competing Interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2019