# Frailty phenotype, frailty index and risk of mortality in Chinese elderly population- Rugao longevity and ageing study

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## ARTICLE INFO

## ABSTRACT

Background: To explore the associations of frailty phenotype and frailty index (FI) defined frailty and pre-frailty with mortality in a Chinese elderly population.

Methods: Data of 1788 community-dwelling elders aged 70–84 years from the ageing arm of Rugao Longevity and Ageing Study, a prospective cohort study, were used. Frailty phenotype was defined using modified Fried's phenotype (FP) criteria and FI was constructed using 45 health deficits. Mortality was ascertained using the Death Registry of Rugao's Civil Affairs Bureau.

Results: During 3-year follow-up, 149 (8.3%) of the 1788 elderly subjects died. For frailty phenotype, about 9.5% of the elderly were frail and 43% were pre-frail. For FI, frail (FI > 0.21) was approximately 27.5%, and pre-frail (FI: 0.1–0.21) was approximately 51.3%. Highest mortality was observed among frail participants defined by both FP and FI criteria (all Log Rank P < 0.05). Frailty defined by the frailty index was associated with a 2.31 fold (95% CI 1.16–4.6) risk of all-cause death compared with robust elderly. Compared with the robust elderly, not only frailty (HR 2.24, 95% CI 1.31–3.83) defined by frailty phenotype but also pre-frailty (HR 1.51, 95% CI 1.03–2.21) was associated with risk of all-cause mortality.

Conclusions: Frailty, defined by either phenotype or index, is associated with increased risks of mortality in elderly Chinese community population.

## 1. Introduction

Frailty, a state of increased vulnerability to minor stressor events and a consequence of cumulative decline in many physiological systems during a lifetime (Morley et al., 2013), was defined most often by a physical frailty phenotype (FP) consisting of five possible components (weight loss, exhaustion, weakness, slowness, and reduced physical activity) (Fried et al., 2001) or a deficit model consisting a number of deficits to create a Frailty Index (FI) (Rockwood & Mitnitski, 2007; Rockwood et al., 2005; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). Recently, a systematic review and meta-analysis (Chang & Lin, 2015) including 11 prospective cohort studies conducted in Europeans found that frailty defined by FP predicts increased risks of future

mortality. However, this review lacks evidence of Chinese population, the exposure pattern and the disease spectrum of which are quite different from those of the Europeans, especially for the elderly adults.

In the year 2018, another systematic review and meta-analysis found that frailty defined by FI was also associated with the risk of mortality in the elderly population (Kojima, Iliffe, & Walters, 2018). This report not only selected cohort studies conducted in Europeans, but also included two Chinese cohort - the Chinese Longitudinal Health and Longevity Study (CLHLS) (Gu et al., 2009; Yang & Gu, 2016) and the Beijing Longitudinal Study of Ageing (BLSA) (Shi et al., 2011; Yu et al., 2012). In a longitudinal study of 4000 Hong kong Chinese individuals aged 65 and older, frailty scores based on frailty phenotypes were found comparable with frailty index in predicting 4-year mortality

and physical limitations (Woo, Leung, & Morley, 2012). More recently, FRAIL, an interview-based simple screening tool based on phenotype model showed superior predictive ability for in-hospital mortality than frailty index among acutely ill hospitalized older adults in Singapore (Chong et al., 2018). However, data of the relationship between frailty phenotype and mortality is scarce in the mainland Chinese population. In the present study, we aimed to observe the effects of frailty and pre-frailty, measured with both FP and FI on three-year all-cause mortality in an elderly Chinese population.

## 2. Methods

### 2.1. Study design and participants

We used data from the ageing arm of the Rugao Longevity and Ageing Study (RuLAS), a community-based prospective study conducted in Rugao, Jiangsu Province, China. As previously described (Liu, Wang, Zhi et al., 2016; Liu, Wang, Zhang et al., 2016), 1788 elderly adults aged 70–84 years were recruited at baseline (November–December 2014, wave1) from 31 rural communities of Jiang'an Township, Rugao City, according to 5-year age and gender strata. Follow-up survey was conducted 1.5 year later (April-June 2016, wave2) and 3 year later (November–December 2017, wave3) for repeated measurements of baseline variables and for morbidity and mortality data collection. A flow chart detailing disposition of the study participants is shown in Supplementary Figure. The Human Ethics Committee of the School of Life Sciences, Fudan University, Shanghai, People's Republic of China, approved the present study. Written informed consent was obtained from all participants prior to the study.

### 2.2. Frailty measurements

Five components including unintentional weight loss, exhaustion, low activity, slowness, and weakness were used to define the frailty phenotype according to Fried criteria (Fried et al., 2001). Similar measurements of the five criteria were used and the detailed description has been described previously (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015). In brief, unintentional weight loss, exhaustion, and low activity were based on self-reported items, including "weight has decreased by 4.5 kg or 5% during the last 12 months", "feeling tired all of the time (at least 3 or 4 days a week)", and "needing help to walk". Slowness was defined as being below the 20th sex-specific percentile in gait speed (assessed by a TUG test). In the TUG test, the study participants were asked to stand up from an armchair, walk 3 m, return, and sit down again. The timing of this test began when the participants back came off the back of the armchair and stopped when their buttocks touched the seat of the chair again (Nordin, Lindelof, Rosendahl, Jensen, & Lundin-Olsson, 2008). Weakness was based on the self-report defined as "having difficulty in lifting or carrying something as heavy as 10 kg", which was similar to that used in previous studies (Blodgett et al., 2015). Any of the above five indicators with any three or more indicators is defined as "frail", any one or two is a pre-frail, and zero is "robust".

According to the standard procedure suggested by Rockwood and Mitnitski (Searle et al., 2008), and Searle et al (Rockwood et al., 2005; Searle et al., 2008), 45 health deficits that include symptoms, co-morbidities, activities of daily living (basic and instrumental), cognitive and psychological function were used to construct a frailty index, and the detailed description was provided previously (Liu, Wang, Zhi et al., 2016; Liu, Wang, Zhang et al., 2016). In brief, each deficit is assigned a score of 0–1 according to the answer to indicate presence or absence of deficit. For example, the question: "Is assistance for meals needed?", and the answer to "completed independently" is 0 points. "Need some help" is 0.5 points, and "full help needed" is 1 point. Accumulate all scores and divide by 45 to get a value of 0–1, which is the clinical frailty index. Since the frailty index is a continuous data variable and

representative, we classify it according to FI $\leq 0.1$, 0.1-0.21, $> 0.21$ (Song, Mitnitski, & Rockwood, 2010; Zhu et al., 2016).

### 2.3. Mortality

We followed up the death data from Jan. 2015 through Dec. 2017 for the studied 1788 participants. Time and cause of death was ascertained using the Death Registry of Rugao's Civil Affairs Bureau. The doctors of the community clinics contacted the family members and checked the date and the cause of death.

### 2.4. Covariates

Covariates include age (70–74 years, 75–79 years and 80–84 years), gender (male and female), smoking habits (never smoked, current smoker, or former smoker), drinking habits (never drank, current drinker, or former drinker), occupation (farmers and others), marital status (currently married, other [never married, divorced, separated, or widowed]), and literacy (illiterate, literate ($\geq 1$ year of education)). The BMI ($kg/m^2$) was calculated by dividing the weight (in kilograms) by the square of the body height (in square meters). Cognitive function was measured by a widely used Hasegawa Dementia Scale-Revised (HDS-R) which includes 11 items that are used to measure orientation, memory, attention/calculation, and verbal fluency (Tsukamoto et al., 2009). The presence of mild cognitive impairment (MCI) was defined by an HDS of $\leq 21.5$.

### 2.5. Statistical analysis

The data were presented as either the mean values $\pm$ SD or the percentages, with comparisons between different groups using $t$-test/Mann–Whitney $U$ test or chi-square test, if appropriate. Kaplan-Meier curves were used to study survival according to frailty groups. Cox proportional hazard regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) adjusting for multiple covariates. Statistical analyses were performed using SPSS statistical software 22.0 (IBM Corporation, Armonk, NY, USA). A two-sided p < 0.05 was considered significant.

## 3. Results

During 3-year follow-up, 149 (8.3%) of the 1788 participants died. One hundred and thirty-seven subjects (7.6%) of the baseline participants did not return for wave 3 examine, but we acquired their information of vital status for survival analysis. Table 1 showed the demographic and health characteristics of participants according to survival status. The average age of the study participants was 75.4 $\pm$ 3.9 years and 53.6% were women. Participants who died from all causes were more likely to be male, elder, and less educated. Frail individuals according to both frailty phenotype and frailty index were more likely to be male, elder, illiterate, smokers, alcohol drinkers, farmers, and mild cognitive impairment (Supplementary Tables S1 and S2).

For frailty phenotype, about 9.5% of the elderly were frail and 43% were pre-frail. 17.5% of the phenotype-defined frailty participants died during three years follow-up compared with 8.7% in the robust group. The mean FI was 0.17 for those lived and 0.19 for those died (p < 0.001). For FI, frail (FI > 0.21) was approximately 27.5%, and pre-frail (FI: 0.1–0.21) was approximately 51.3%.

Fig. 1 shows the Kaplan-Meier survival curve of the all-cause mortality according to FP and FI categories. For frailty phenotype, the highest mortality was observed among frail participants (Log Rank P < 0.001). For frailty index, the highest mortality was observed in frail participants with a FI > 0.21 (Log Rank P = 0.041).

Table 2 shows the association analyses of FI and FP with three-year mortality. Frailty defined by the frailty index was associated with a 2.31

**Table 1**

Demographic and health characteristics of participants according to survival status.

| Characteristics | Total | Lived | Died from All Causes | P |
|---|---|---|---|---|
| N(%) | 1788 | 1639(91.7) | 149(8.3) | |
| **Sex (%)** | | | | 0.018 |
| Male | 830(46.4) | 747(45.6) | 83(55.7) | |
| Female | 958(53.6) | 892(54.4) | 66(44.3) | |
| **Age Group** | | | | 0.018 |
| 70–74 | 854(47.8) | 797(48.6) | 57(38.3) | |
| 75–79 | 618(34.6) | 563(34.4) | 55(36.9) | |
| 80–84 | 316(17.7) | 279(17) | 37(24.8) | |
| **Diabetes** | | | | 0.25 |
| No | 1538(88.4) | 1414(88.7) | 124(85.5) | |
| Yes | 201(11.6) | 180(11.3) | 21(14.5) | |
| **Hypertension** | | | | 0.235 |
| No | 368(20.8) | 332(20.5) | 36(24.7) | |
| Yes | 1398(79.2) | 1288(79.5) | 110(75.3) | |
| **Marital Status, N (%)** | | | | 0.254 |
| Currently Married | 608(34.3) | 551(33.9) | 57(38.5) | |
| Others | 1167(65.8) | 1076(66.1) | 91(61.5) | |
| **Education Level, N (%)** | | | | 0.045 |
| Illiterate | 940(53.5) | 872(54.2) | 68(45.6) | |
| Literate | 818(46.5) | 737(45.8) | 81(54.4) | |
| **Smoking Status (%)** | | | | 0.550 |
| Never | 1314(74.5) | 1210(74.8) | 104(70.8) | |
| Current | 255(14.5) | 231(14.3) | 24(16.3) | |
| Ever | 195(11.1) | 176(10.9) | 19(12.9) | |
| **Alcohol Consumption (%)** | | | | 0.290 |
| Never | 1251(70.8) | 1142(70.5) | 109(73.7) | |
| Current | 332(18.8) | 311(19.2) | 21(14.2) | |
| Ever | 184(10.4) | 166(10.3) | 18(12.2) | |
| **Occupation (%)** | | | | 0.982 |
| Farmer | 1585(88.7) | 1453(88.7) | 132(88.6) | |
| Others | 203(11.4) | 186(11.4) | 17(11.4) | |
| **BMI (%)** | | | | 0.720 |
| < 18.5 | 852(48.1) | 781(48.1) | 71(49) | |
| 18.5–23.9 | 66(3.7) | 59(3.6) | 7(4.8) | |
| > 24 | 852(48.1) | 785(48.3) | 67(46.2) | |
| **MCI (%)** | | | | 0.229 |
| HDR-S > 21.5 | 826(46.8) | 764(47.2) | 62(41.9) | |
| HDR-S ≤ 21.5 | 940(53.2) | 854(52.8) | 86(58.1) | |
| **Frailty Index** | | | | 0.069 |
| < =0.1 | 376(21.2) | 349(21.5) | 27(18.1) | |
| 0.1 -0.21 | 910(51.3) | 841(51.8) | 69(46.3) | |
| > 0.21 | 488(27.5) | 435(26.8) | 53(35.6) | |
| **Frailty phenotype** | | | | < 0.001 |
| robust | 851(47.6) | 805(49.1) | 46(30.9) | |
| pre-frail | 768(43) | 691(42.2) | 77(51.7) | |
| Frail | 169(9.5) | 143(8.7) | 26(17.5) | |
| **Mean, SD** | | | | |
| Age, year | 75.4 ± 3.9 | 75.3 ± 3.9 | 76.4 ± 4.3 | 0.001 |
| Frailty Index | 0.17 ± 0.09 | 0.17 ± 0.09 | 0.19 ± 0.1 | 0.006 |
| Frailty phenotype | 0.89 ± 1.06 | 0.85 ± 1.04 | 1.28 ± 1.11 | < 0.001 |
| BMI, kg/m$^2$ | 24.1 ± 3.54 | 24.12 ± 3.52 | 23.9 ± 3.77 | 0.477 |

Continuous variables are expressed as mean ± standard deviation, categorical variables are expressed as percentages, and chi-square test is used for categorical variables.

fold (95% CI 1.16–4.6) risk of mortality compared with robust elderly. For frailty phenotype, not only frailty (HR 2.24, 95% CI 1.31–3.83) but also pre-frailty were associated with risk of all-cause mortality (HR 1.51, 95% CI 1.03–2.21). The aforementioned associations remain significant after adjustments of multiple factors including age, gender, marital status, education level, smoking status, drinking status, body mass index, hypertension, diabetes, and cognitive function.

## 4. Discussion

In the present study, we observed that frailty defined by frailty index was associated with increased risk of three-year mortality in the Rugao ageing cohort population aged 70–84 years. In addition, for the first time, we found that frailty and pre-frailty defined by phenotype was associated with mortality in the mainland Chinese population.

Associations between phenotype defined frailty and increased risk of future death were reported in observational studies conducted in the western elderly populations (Graham et al., 2009; Klein, Klein, Knudtson, & Lee, 2005; Mitnitski et al., 2005). A systematic review and meta-analysis including 11 prospective studies of Europeans and U.S. populations showed that compared with robust older adults, older people with frailty have the highest risks of mortality, followed by older people with pre-frailty (Chang & Lin, 2015). In the year 2018, based on data of the National Health and Nutrition Examination Survey (NHANES), Crow et al. (2018) found that 40.3% of the studied US population aged 60 and older (mean age 71.1 ± 0.19, 56% female) is pre-frail and 9.2% is frail. In this elderly U.S. population, pre-frail (HR 1.64, 95% CI, 1.45–1.85) and frail (HR 2.79, 95% CI 2.35–3.30) participants had a greater risk of death and of cardiovascular death (pre-frail: HR 1.84, 95% CI 1.45–2.34; frail: HR 3.39, 95% CI 2.45–4.70). The prevalence of pre-frailty (43%) and frailty (9.5%) and the magnitude of the association of pre-frailty (HR 1.51,95% CI 1.03–2.21) and frailty (HR 2.24, 95% CI 1.31–3.83) with mortality is comparable to our Rugao Ageing cohort population aged 70–84 years (mean age 75.4 ± 3.9 years, female 53.6%).

Frailty index-defined frailty was found associated with increased risk of future mortality both in western and Chinese populations, using different cut point of frailty index. Recently, a systematic review and meta-analysis including 13 prospective cohort studies (mostly conducted in European and American populations) showed that higher FI was associated with higher mortality risk with a pooled HR of 1.282 (95% CI = 1.258–1.307) per 0.1 FI increase (Yang & Gu, 2016). For Chinese population, observations conducted in the Chinese Longitudinal Health and Longevity Study (CLHLS) (Yang & Gu, 2016) showed that the third and fourth FI quartiles have higher proportions of death than those in the first or second quartiles in elders over 65 years of age. Another study using data of the CLHLS found that during a period of a 3-year follow-up, transitions to greater frailty and remaining frail had significantly higher risks of death and types of death (defined by 30 bedridden days and suffering) compared with remaining non-frail and pre-frail (Liu et al., 2018). A study using data of the Beijing Longitudinal Study of Aging (Shi et al., 2011) showed that increasing grades of the FI have a dose response effect in relation to eight year survival, with > 90% mortality of the most frail (FI > 0.5). In our study, we categorized FI into pre-frail and frail group and found that baseline frailty status, instead of pre-frailty, was associated with increased risk of future mortality.

Interestingly, only phenotype defined pre-frailty was found associated with 3-year mortality and index defined pre-frailty was not associated with it in our study population. Better accuracy in predicting mortality have been found for frailty index than for frailty phenotype (Kulminski et al., 2008; Rockwood, Andrew, & Mitnitski, 2007). Recently, FRAIL, a simple frailty measure based on frailty phenotype model, was found comparable with FI in predicting mortality in Hong kong Chinese (Woo et al., 2012) and Singapore Chinese (Chong et al., 2018). These observations support the clinical utility of phenotype based frailty measures. In a previous study (Zhu et al., 2016), we found a fair agreement between our FI and FP instruments, as manifested with a kappa agreement of 0.310 (95% CI: 0.277 utilit. However, although FI and FP have notable statistical convergence (Rockwood et al., 2007), the conceptual differences between FI and FP may help explain the different associations of them with mortality among different studies. Alternatively, our FI is mainly based on self-reported information, some variables like disease diagnosis included in the FI may be biased,
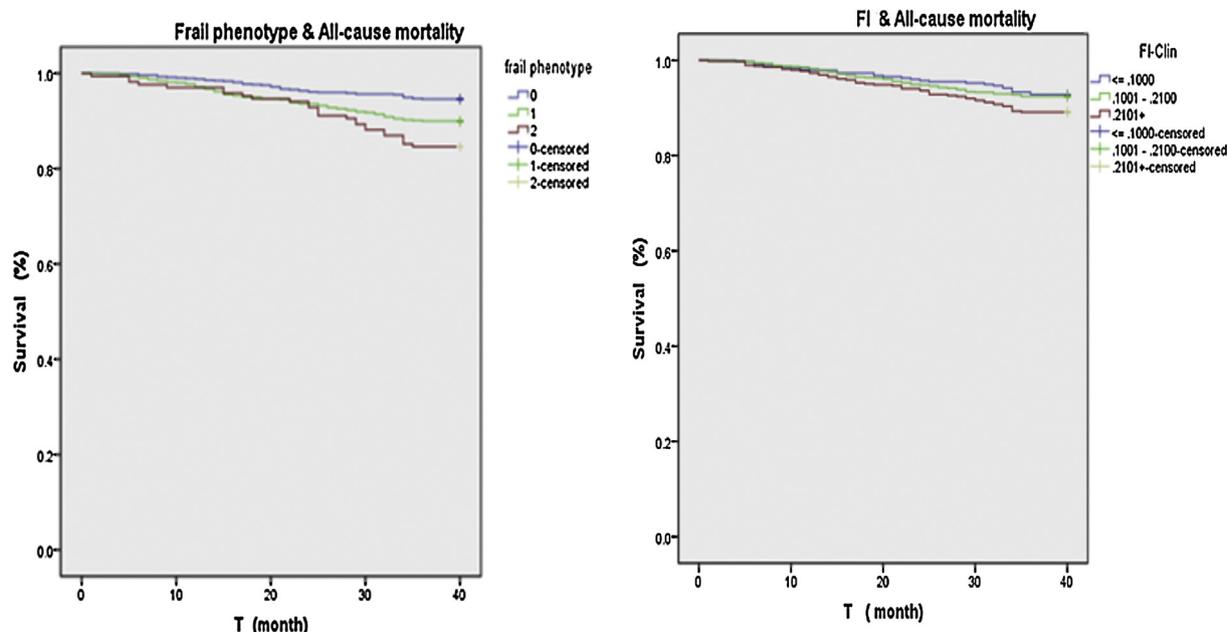
**Fig. 1.** Kaplan-Meier survival curve analysis of the all-cause mortality according to FP and FI categories.

**Table 2**
Regression analysis of COX risk proportional model of frailty and all-cause mortality.

| | Model1 HR(95%CI) | P | Model2 HR(95%CI) | P | Model3 HR(95%CI) | P |
|---|---|---|---|---|---|---|
| **FI-Clin** | | | | | | |
| Robust | 1(ref.) | | 1(ref.) | | 1(ref.) | |
| Pre-frail | 1.11(0.62–1.99) | 0.719 | 1.23(0.68–2.21) | 0.497 | 1.19(0.66–2.16) | 0.564 |
| Frail | 1.96(1.04–3.69) | 0.038 | 2.22(1.13–4.33) | 0.02 | 2.31(1.16–4.6) | 0.017 |
| **Frailty Phenotype** | | | | | | |
| Robust | 1(ref.) | | 1(ref.) | | 1(ref.) | |
| Pre-frail | 1.68(1.17–2.40) | 0.005 | 1.71(1.19–2.47) | 0.004 | 1.51(1.03–2.21) | 0.036 |
| Frail | 2.57(1.60–4.12) | < 0.001 | 2.68(1.64,4.40) | < 0.001 | 2.24(1.31–3.83) | 0.003 |

Model 1 was an unadjusted model when calculating related risks using the Cox-risk ratio model, whereas Model 2 was adjusted for covariates such as age and gender on the basis of Model 1. Model 3 adjusted for covariates such as the marital status, education level, smoking status, drinking status, body mass index, hypertension, diabetes, and mild cognitive impairment on the basis of model 2.

depending on local norms. This limitation of our study may also be a reason why index defined pre-frailty was not associated with mortality in our cohort population. Another reason that FI defined pre-frailty was not associated with mortality risk in our study may due to lack of statistic power of FI to discriminate the relative little outcome events followed only three years at this stage.

## 5. Conclusions

In summary, we found that frailty, defined by either phenotype or frailty phenotype, is associated with increased risks of mortality in elderly community Chinese population. Frailty screening using FI, and frailty and pre-frailty screening using FP may be useful in elderly community population since classifying community population into pre-frailty and frailty threshold is helpful for early intervention.

## Conflict of interests

The authors declare that they have no competing interests.

All authors have read and approved the manuscript submitted. No part of the submitted work has been published or is under consideration for publication elsewhere, in whole or in part, in any language. There are no competing financial interests.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2018.11.001.

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