Cognitive Frailty and Adverse Health Outcomes: Findings From the Singapore Longitudinal Ageing Studies (SLAS)

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Abstract

Objectives: There is a recent consensus proposal of “cognitive frailty” defined by the presence of both physical frailty and cognitive impairment in the absence of dementia. The relevance, validity, and utilization of cognitive frailty, however, is presently unclear. We determine whether concurrent physical frailty and cognitive impairment, compared with physical frailty alone substantially increased adverse health outcomes (functional disability, hospitalization, poor quality of life [QOL], and mortality).

Design: Longitudinal study.


Participants: Two thousand three hundred seventy-five Chinese Singaporeans aged 55 and above without dementia and degenerative disorders.

Measurements: The associations of physical frailty (Cardiovascular Health Study criteria: \(0 = \text{robust}, 1-2 = \text{pre-frail}, 3-5 = \text{frail}\)) with and without cognitive impairment (mini-mental state examination \(<26\)) and adverse outcomes were estimated, controlling for age, gender, education, comorbidity, smoking, alcohol consumption, depressive symptoms, baseline activities of daily living-instrumental and basic activities of daily living disability or QOL score.

Results: Compared to robust noncognitively impaired individuals, physical pre-frailty with cognitive impairment was associated with a twofold increased prevalence and incidence of functional disability, a twofold increased incidence of poor QOL, and 1.8-fold increased mortality risks. Cognitively impaired frail individuals stood out with 12- to 13-fold increased prevalence and incidence of functional disability, a five- and 27-fold increased prevalence and incidence of low QOL, and a fivefold increased mortality risk. The estimated prevalence of physical frailty with cognitive impairment was 1.8%, and physical pre-frailty with cognitive impairment was 8.9%.

Conclusion: Pre-frailty and frailty with impaired cognitive function, found in 10.7% of this dementia-free population, was associated with an evidently high risk of adverse health outcomes.

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Frailty is a commonly recognized geriatric syndrome resulting in adverse health outcomes including hospitalization, institutionalization, falls, functional disability, and mortality.\cite{1-3} Frailty results from age-related, cumulative decline in multiple physiological systems, including the brain, endocrine, immune, and skeletal muscle. Sarcopenia, a progressive loss of skeletal muscle mass, strength, and power, the Singapore Longitudinal Ageing Study was supported by two grants (No. 03/12/17/214 and No. 08/12/19/567) from the Biomedical Research Council, Agency for Science,Technology and Research in Singapore.

Authors’ contributions: T.-P. Ng reviewed the literature, formulated the hypothesis, designed the study, interpreted the results, and drafted and reviewed the manuscript.

L. Feng reviewed the literature, performed the data analysis, interpreted the results, and drafted and reviewed the manuscript.

M.S.Z. Nyunt, Q. Gao, L. Feng, and K.B. Yap participated in the design and conduct of the study, collection of data, interpretation of the results, and review of the manuscript.

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is a key component of frailty, which is widely defined as a physical phenotype using Cardiovascular Health Study criteria (CHS): shrinking, weakness, slowness, fatigue, and inactivity. This physical phenotype has shown strong predictive validity for adverse health outcomes. Given the heterogeneous nature of frailty, cognitive impairment (which is also associated with functional decline and disability) is arguably a component of frailty. Research is needed to determine the contribution of other clinical domains to frailty that might improve the predictive value of the frailty phenotype. Recently, an international consensus group has proposed the concept of “cognitive frailty” as a heterogeneous cognitive condition characterized by the simultaneous presence of both physical frailty and cognitive impairment, excluding concurrent dementia or other dementias. There is uncertainty about the meaning, validity, relevance, and utilization of cognitive frailty in the clinical setting. Empirical support for the concept of cognitive frailty should derive from data that show the close association of physical frailty and cognitive impairment and its prognostic utility in predicting future risks of adverse health outcomes, including cognitive, functional disability, health service use, and mortality outcomes.

There is currently good evidence to show that physical frailty is strongly associated with prevalent cognitive impairment and dementia in cross-sectional studies and with subsequent cognitive decline or development of mild cognitive impairment or dementia in some but not all longitudinal studies. One study reported that cognitive impairment incorporated into the physical frailty phenotype improved considerably its predictive validity for noncognitive adverse outcomes including disability, hospitalization, and mortality more than physical frailty alone. We have recently reported that physical frailty was associated with increased prevalence and incidence of cognitive impairment, and coexisting physical frailty and cognitive impairment conferred additionally greater risk of incident mild cognitive impairment and dementia. In this study, we further analyzed data in this population-based prospective cohort study (Singapore Longitudinal Ageing Study, SLAS) to determine whether concurrent physical frailty and cognitive impairment, compared with physical frailty alone, substantially increased the risk of mortality, functional disability, hospitalization, and impaired quality of life (QOL).

Methods

Participants

As previously detailed, the SLAS-1 is a population-based longitudinal study of aging and health of community-dwelling older Singaporeans aged 55 and above, excluding individuals who were not able to participate because of severe physical or mental disability. The cohort members were first recruited in 2003/2005, and completed 2 follow-ups at approximately 3-year intervals up to December 31, 2009. Baseline data included demographic, medical, behavioral, biological, psychosocial, and neurocognitive characteristics collected from extensive questionnaire interviews and assessments. The study was approved by the National University of Singapore Institutional Review Board, and written informed consent was obtained from all participants.

We recruited at baseline 2804 older adults for the SLAS-1 cohort. In this study, we excluded a small number of non-Chinese (n = 193) and those who reported a history of dementia, stroke, Parkinson’s disease, other neurodegenerative disorders (n = 133), and missing baseline frailty score (n = 73), Mini-Mental State Examination (MMSE) score (n = 3), physical function (n = 20) smoking (n = 3), as well as a National Registration Identity Card number (n = 4), resulting in 2375 Chinese older adults for cross-sectional analysis.

The longitudinal analyses for different adverse health outcomes were based on various sample sizes given missing data on baseline covariates and from follow-up loss:

1. Mortality outcome: the analytic sample (N) comprised 2375 individuals.
2. Functional activities of daily living-instrumental and basic activities of daily living (ADL-IADL) disability outcome: N = 1207 individuals after excluding those with missing baseline (n = 20) and follow-up (n = 849) physical function data, baseline smoking status (n = 1), and those with dependent physical function at baseline (n = 325).
3. Hospitalization outcome: N = 1503 individuals, after excluding participants missing follow-up hospitalization data (n = 828), baseline data on physical function (n = 12), smoking status (n = 1), or hospitalized in the year prior to baseline (n = 58).
4. Health-related QOL Short Form-12 (SF-12) physical component score (PCS): N = 1197 after excluding those without follow-up SF-12 data (n = 827), baseline data on SF-12 (n = 4), physical function (n = 12), smoking status (n = 1), and those with baseline PCS lower than its lowest quartile (n = 361).

Baseline Measurements

Physical frailty at baseline was assessed based on criteria used in the CHS with operational modifications:

1. Shrinking was defined as body mass index of <18.5 kg/m² or weight loss of >4 kg in the past 6 months.
2. Weakness was assessed by the Performance-Oriented Mobility Assessment battery. Muscle weakness was assessed by performance on rising from a chair in the sitting position with arms folded. The summed score (range, 0-16) in the lowest gender- and body mass index-adjusted quintile was used to denote weakness and instability.
3. Slowness was determined with the subject walking 6 meters and returning quickly to the starting point and denoted by gait performance scores (range, 0-12) of less than 9.
4. Exhaustion was measured by one question from the SF-12 QOL scale: “Do you have lots of energy?”
5. Low activity was assessed by questions on the number and frequencies of usual participation in 16 categories of activities using the 3-point Likert scale for each activity, and low activity was defined as a total score below the lowest gender-adjusted quintile.

Scores were assigned to each frailty component (1 = present, 0 = absent), and the summed scores were used to categorize subjects as frail (score = 3-5), pre-frail (score = 1 or 2), and robust (score = 0 points). This modified categorical measure of physical frailty has been shown in previous studies to predict depression, ADL-IADL dependency, hospitalization, and poor QOL.

Cognitive impairment was determined using scores of the Chinese version of the Mini-Mental State Examination (CMMSE), with total scores ranging from 0 to 30 (higher score indicating better cognition). The CMMSE has been validated for local use in Singaporean older adults, and a score of <26 denotes mild or greater degrees of cognitive impairment.

Outcome Measurements

1. Functional disability was assessed by self-reported measures of IADL and ADL. Participants were classified as having any IADL or ADL disability and as no IADL or ADL disability.
2. QOL was measured using the Medical Outcomes Study SF-12 PCS of QOL. Poor QOL was defined by the PCS score below the lowest quartile in the distribution.
3. Hospitalization was determined by the participants’ self-reports of new hospitalizations for any chronic medical conditions over the previous year.
alcohol consumption. Depressive symptoms were determined by the Geriatric Depression Scale (GDS). Other lifestyle variables included self-reports of current smoking and medical comorbidities. Medical comorbidities were determined by responses to a checklist of secondary or other medical condition(s) (depression excluded) in the past year and estimating the total number of medical conditions.

### Other Variables

Sociodemographic data included age, gender, and education. Medical comorbidity was determined by responses to a checklist of secondary or other medical condition(s) (depression excluded) in the past year and estimating the total number of medical conditions. Lifestyle variables included self-reports of current smoking and daily alcohol consumption. Depressive symptoms were determined by the Geriatric Depression Scale (GDS), which has been validated for use in local Chinese, Malay, and Indian subjects. The presence of depressive symptoms was denoted by a GDS score of 5 or above.

### Statistical Analysis

We performed cross-sectional and longitudinal analyses of the associations of frailty with adverse outcome variables using logistic regression for ADL-IADL disability, hospitalization and low QOL outcomes, and Cox-regression analyses for mortality outcomes. We estimated odds ratios (ORs) or hazard ratios (HRs) of association and estimated ORs and HRs were adjusted as appropriate for age, gender, education, medical comorbidity, current smoking, alcohol consumption, depressive symptoms, and as appropriate baseline ADL-IADL disability, baseline PCS score (for PCS as outcome). A two-sided P value of .05 was considered as statistically significant in the study. All analysis was performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

### Results

The mean age of the study sample was 65.8 (±7.46 SD), 63.8% were female, 51.8% had primary or lower education, and 20% had cognitive impairment at baseline. About 2.6% were frail, 33.4% pre-frail, and 64.1% robust overall. Cognitive impairment was present in 15% of robust, 27% of pre-frail, and 70% of frail participants. The baseline characteristics of the Chinese older adults are shown in Table 1. Compared with robust participants, those who were pre-frail and frail were older, had a lower education level, a higher proportion of current smokers but a lower proportion of current drinkers. They also had more medical comorbidities and greater prevalence of cognitive impairment and depressive symptoms at baseline.

### Physical Frailty and Adverse Health Outcomes

The associations between physical frailty (robust, pre-fraility and frailty) and prevalent adverse health status from cross-sectional analyses are shown in Table 2. Compared to being robust, being pre-frail...
### Table 3
Associations of Baseline Coexisting Physical Frailty and Cognitive Impairment With Prevalent and Follow-Up Adverse Health Events

<table>
<thead>
<tr>
<th>ADL-IADL Disability</th>
<th>Past Year Hospitalization</th>
<th>Lowest Quartile of PCS-12</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Cross-sectional analyses</td>
<td>N = 2375</td>
<td></td>
<td>N = 2375</td>
</tr>
<tr>
<td>Robust without cognitive impairment</td>
<td>0.74 (0.47-1.15)</td>
<td>.18</td>
<td>22/21</td>
</tr>
<tr>
<td>Pre-frail without cognitive impairment</td>
<td>200/1301</td>
<td>1.00</td>
<td>51/1301</td>
</tr>
<tr>
<td>Pre-frail with cognitive impairment</td>
<td>20/1301</td>
<td>0.74 (0.47-1.15)</td>
<td>.18</td>
</tr>
<tr>
<td>Frail without cognitive impairment</td>
<td>36/43</td>
<td>12.6 (5.25-30.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frail with cognitive impairment</td>
<td>36/43</td>
<td>12.6 (5.25-30.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Robust (with or without cognitive impairment)</td>
<td>230/1552</td>
<td>1.00</td>
<td>47/1522</td>
</tr>
<tr>
<td>Pre-frail or frail without cognitive impairment</td>
<td>30/212</td>
<td>0.74 (0.47-1.15)</td>
<td>.18</td>
</tr>
<tr>
<td>Pre-frail or frail with cognitive impairment</td>
<td>30/212</td>
<td>0.74 (0.47-1.15)</td>
<td>.18</td>
</tr>
<tr>
<td>Longitudinal analyses</td>
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<td></td>
<td>N = 2371</td>
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<td>Robust without cognitive impairment</td>
<td>0.74 (0.47-1.15)</td>
<td>.18</td>
<td>22/21</td>
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<tr>
<td>Pre-frail without cognitive impairment</td>
<td>169/580</td>
<td>1.77 (1.38-2.27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-frail with cognitive impairment</td>
<td>169/580</td>
<td>1.77 (1.38-2.27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frail without cognitive impairment</td>
<td>9/18</td>
<td>2.75 (1.00-7.58)</td>
<td>.050</td>
</tr>
<tr>
<td>Frail with cognitive impairment</td>
<td>9/18</td>
<td>2.75 (1.00-7.58)</td>
<td>.050</td>
</tr>
<tr>
<td>Robust (with or without cognitive impairment)</td>
<td>230/1552</td>
<td>1.00</td>
<td>47/1522</td>
</tr>
<tr>
<td>Pre-frail or frail without cognitive impairment</td>
<td>178/598</td>
<td>1.87 (1.47-2.38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-frail or frail with cognitive impairment</td>
<td>178/598</td>
<td>1.87 (1.47-2.38)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; IADL, instrumental activities of daily living; OR, odds ratio; PCS, physical component score; HR, hazard ratio; SF-12, Short Form-12; 95% CI, 95% confidence interval.

Cognitive impairment was denoted by MMSE < 26. Adjusted for age, gender, education, medical comorbidity, current smoking, alcohol drinking, depressive symptoms, baseline ADL-IADL disability, baseline MMSE score, baseline PCS score (for PCS as outcome).

*Longitudinal analysis were restricted to subjects without baseline ADL-IADL disability or low PCS or hospitalization for respective outcomes.
and frail were associated with increased ORs (between 1.41 and 6.33) for prevalent disability and low QOL, but not for hospitalization in the past year. In longitudinal analyses, frail participants compared to robust participants were significantly more likely to subsequently report disability (OR, 7.21; 95% CI, 1.72-30.3), poor QOL (OR, 6.27; 95% CI, 1.91-20.6), and to die earlier (HR, 2.56; 95% CI, 1.56-4.19). Pre-frailty was associated with moderately elevated risks of incident adverse events (ORs ranging from 1.38 to 1.66), which was significant for only poor QOL (OR, 1.66; 95% CI, 1.20-2.30).

**Physical Frailty with Cognitive Impairment and Adverse Health Outcomes**

Table 3 shows the results of cross-sectional and longitudinal analyses (also in Figure 1) of the associations between subcategories of physical frailty with and without cognitive impairment (MMSE < 26) and adverse health outcomes, using robust and noncognitively impaired participants as the reference group.

**ADL-IADL Disability**

In cross-sectional and longitudinal analyses, the estimates of ORs were increased for pre-frailty without cognitive impairment: OR = 1.77 (95% CI, 1.38-2.27) for prevalent disability and OR = 1.37 (95% CI, 0.84-2.24) for incident disability, and frailty without cognitive impairment: OR = 2.75 (95% CI, 1.00-7.58) for prevalent disability and OR = 5.46 (95% CI, 0.69-43.3) for incident disability. The estimates of increased ORs were much greater in the presence of cognitive impairment, for pre-frailty with cognitive impairment: OR = 2.43 (95% CI, 1.69-3.49) for prevalent disability and OR = 2.04 (95% CI, 1.00-4.14) for incident disability, and frailty with cognitive impairment: OR = 12.6 (95% CI, 5.25-30.4) for prevalent disability, and OR = 12.2 (95% CI, 1.69-88.5) for incident disability.

**Quality of Life**

In both cross-sectional and longitudinal analyses, similar patterns of associations of poor QOL with subcategories of physical frailty with and without cognitive impairment were observed. Frailty with cognitive impairment in particular was most strongly associated with poor QOL at baseline (OR, 5.34; 2.42-11.7) and from follow-up (OR, 26.9; 3.05-238.4).

**Mortality**

Compared to being robust without cognitive impairment, being pre-frail without cognitive impairment (HR, 1.40; 95% CI, 1.00-1.94) and frail without cognitive impairment (HR, 1.49; 95% CI, 0.53-4.20) were associated with an approximate 50% increased risk of dying. Being pre-frail with cognitive impairment was associated with an 80% greater risk of dying (HR, 1.83, 95% CI; 1.20-2.79), but frailty with cognitive impairment was associated with a fivefold increased risk of death (HR, 5.12; 95% CI, 3.00-8.74).

**Discussion**

Previous studies have shown that the physical frailty phenotype predicted an increased risk of cognitive decline and dementia. Likewise, we have previously shown that coexisting physical frailty and cognitive impairment conferred an additionally greater risk of prevalent and incident mild cognitive impairment and dementia. In this study, we showed that frail and pre-frail individuals with cognitive impairment compared to their cognitively normal counterparts were more likely to have a substantially higher prevalence and incidence of functional disability, poorer QOL, and mortality. In particular,
those who were cognitively impaired and frail (cognitive frail) stood out for their 12-fold increased prevalence and incidence of functional disability, five- and 27-fold increased prevalence and incidence of low QOL status, and fivefold increased mortality risk. Cognitive pre-frailty was also associated with a twofold increased prevalence and incidence of functional disability, a twofold increased incidence of low QOL status, and a 1.8-fold increase in mortality risks.

Our study corroborates prior findings from the Three-City Study and suggests that adding cognitive impairment to the operational criteria defining the frailty phenotype could improve the definition and increase its predictive validity with regard to adverse health outcomes. In that study, cognitively impaired frail persons showed a significantly increased risk of developing dementia and functional disability and a marginally greater risk of incident hospitalization, but no significant increase in mortality, although there was a positive trend in mortality across cognitively impaired robust, pre-frail, and frail groups.

Semi-automatically, the combination of physical frailty and cognitive impairment needs to be more clearly understood. It is widely accepted that frailty is broadly characterized by loss of physiological reserve involving multiple systems. Cognitive impairment is logically a component of frailty, and in accord with the cumulative deficit model, is operationalized as a component of the Frailty Index (FI). The addition of cognitive impairment to the physical frailty phenotype thus incorporates the loss of brain and cognitive functioning reserve in the frailty definition. At the same time, the simultaneous presence of both physical frailty and cognitive impairment, excluding concurrent dementia or other dementia has been labelled as cognitive frailty by an international consensus group. As such, cognitive frailty is conceived as a heterogeneous cognitive condition that results from physical frailty per se and not from a known neurodegenerative disorder, and thus, it is regarded as a premorbid entity predicting the risk of dementia. As participants with neurodegenerative disorders and dementia were excluded in this study, pre-frail and frail individuals with cognitive impairment may be considered representative of the cognitive frailty phenotype. At the same time, individuals with both physical frailty and cognitive impairment may be viewed as representing a subset of frail older persons who are most vulnerable to adverse outcomes including dementia, functional disability, and death.

The clinical utility and relevance of our findings should be assessed in relation to the population prevalence of physical frailty and pre-frailty with cognitive impairment. In this population of community-living older persons, approximately 3% and 33% of the participants were frail and pre-frail. Approximately 70% of frail and 27% of pre-frail individuals were cognitively impaired, considerably more than the 15% among robust individuals. The estimated prevalence of coexisting physical frailty and cognitive impairment in this population of older adults without dementia was 1.8%, and physical pre-frailty with cognitive impairment was 8.9%. Given the demonstrable risk of adverse health outcomes associated with physical pre-frailty and frailty with cognitive impairment, potentially a total of 10.7% of the population who are pre-frail or frail and cognitively impaired should be considered as one target group for special intervention. Physical and cognitive frailty are potentially reversible, and research in this direction should provide evidence-based guidance to prevent dementia, functional decline, and premature deaths.

Conclusion

The study has some limitations. We used criteria to define frailty that differ slightly from the ones originally used (eg, the use of a self-reported measure of strength—difficulty rising from a chair instead of the hand grip or lower limb strength). We have shown in another (SLAS-2) cohort that also measured limb strength that both the original and modified CHS scale demonstrated reasonable agreement (weighted kappa of 0.63) and were equally predictive of adverse health outcomes with comparable areas under the curve in receiver operating characteristic ROC analyses. As hospitalization outcome data were based on self-reports of hospitalization episodes and not on electronic hospitalization record linkage, they may not be sufficiently reliable. A MMSE score of 26 as the cut point could overestimate the prevalence of cognitive impairment, slightly biasing the results away from the null. Because participants who were lost to follow-up more likely were males, had more comorbidities, functional disability, depressive symptoms, and were more cognitively impaired, the study may be biased by selecting those who were healthier at baseline, and this may possibly weaken the predictive validity for nonfatal outcomes.

In conclusion, physical pre-frailty and frailty concurrent with cognitive impairment found in 10.7% of this dementia-free population was associated with evidently high risk of adverse health outcomes.

References


