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The effects of frailty and cognitive impairment on 3-year mortality in older adults

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ABSTRACT

Objectives: Frailty and cognitive impairment in late life increase the risk of mortality. Physical frailty is closely associated with cognitive impairment. The aim of the study was to examine the independent and interaction effects of frailty and cognitive impairment in predicting mortality.
Study design: A nationally representative sample of community-dwelling Koreans aged 65 years and older (n = 11,266) was followed for 3 years.
Main outcome measures: Frailty was categorized using Fried's phenotype model. Cognitive impairment was defined as more than 1.5 standard deviations below the age-, gender-, and education-specific norm of the Mini-Mental State Examination. Cox proportional hazards regression was used to analyze the mortality risk by frailty status and the moderating effect of cognitive impairment.
Results: Frailty was associated with cognitive impairment, with 922 (19.1%), 1609 (28.1%), and 392 (42.8%) of the nonfrail, prefrail, and frail group, respectively, being cognitively impaired. Compared with the nonfrail group, those who were prefrail (hazard ratio [HR] = 1.38; 95% confidence interval [CI]: 1.10, 1.73) and frail (HR = 1.78, 95% CI: 1.29, 2.46) had higher mortality rates, after adjusting for sociodemographic variables, health behaviors, and chronic conditions. Cognitive impairment was associated with a 30% increased mortality rate. A significant interaction between frailty and cognitive impairment was observed (p = 0.003). Compared with those nonfrail and not cognitively impaired, frail persons with cognitive impairment had a lower survival rate (HR = 1.92, 95% CI: 1.26, 2.93).
Conclusions: Frailty was a significant predictor of 3-year mortality in community-dwelling older adults, with the association being moderated by baseline cognitive status. Taking cognitive function into account may allow better prediction of adverse outcomes of frailty in later life.

1. Introduction

Life expectancy in developed countries continues to increase, especially for South Korea where average life expectancy for women is expected to be higher than 90 years in 2030 [1]. A significant drawback to the gains in longevity, however, is the elevated risk of frailty and cognitive impairment with age. Frailty is highly prevalent in older age [2] and increases the risk of adverse outcomes, including death [3]. Rapid population aging and extended life expectancy in East Asia are further expected to increase dementia prevalence [4]. Age-associated cognitive decline and impairment have also been shown to be associated with an increased mortality [5]. Thus, identification and management of frailty and cognitive impairment are essential for enhancing health in later years.

A review of evidence suggests a strong association between frailty and cognitive impairment [6]. Higher rates of cognitive impairment have been reported among older adults with increased levels of frailty [7]. In longitudinal studies, physical frailty has been found to predict a higher incidence of cognitive impairment [8]. Alternatively, cognitive impairment raises the risk of incident frailty [9]. Physical frailty and

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cognitive impairment often co-occur, with the term “cognitive frailty” having been coined to describe the simultaneous presence of both conditions [10].

However, the association of frailty and cognitive impairment with mortality is still unclear. Studies have reported frailty and cognitive impairment to predict mortality, but when both were entered in the model only frailty remained significant [11,12]. In contrast, a French study reported that frailty was not a significant predictor of mortality [13]. Much less is known about whether cognitive impairment moderates the relationship between frailty and mortality. Though adding cognitive impairment in the model has been reported to increase the predictive value of frailty on mortality [13], others have found no significant interaction effects between frailty and cognitive impairment in predicting mortality [14]. Clarifying the role of cognitive impairment in the link between frailty and mortality will help to identify older adults at risk of adverse outcomes and to guide appropriate intervention strategies.

The aim of this study was to examine the association of frailty and cognitive impairment with mortality in community-dwelling older adults. We hypothesize that cognitive impairment and frailty independently predicts mortality, and that cognitive impairment acts as an effect modifier in the relationship between frailty and mortality. Given that cognitive impairment is closely associated with frailty, the risk of mortality among the prefrail and frail elderly would be elevated for individuals with cognitive impairment.

2. Methods

2.1. Data source

We analyzed data from the 2008 Living Profiles of Older People Survey (LPOPS), a nationally representative sample of those aged 60 years and older living in the community in the Republic of Korea [7,15]. LPOPS employed stratified two-stage cluster sampling, with the primary sampling unit based on the 2005 census frame and the secondary sampling units consisting of households of older residents. In-person, household interviews of 15,146 individuals were completed by trained interviewers, with an overall response rate of 79.7%. Participants aged 65 years and older (n = 12,087) were considered as the study population, and after excluding those with missing data, the final analytical sample amounted to 11,266 (Supplemental Fig. 1). Informed consent was obtained from all study participants. The study protocol was approved by the Institutional Review Board at Keimyung University, which administered the survey.

2.2. Measurements

A modified Fried’s phenotype model based on the Cardiovascular Health Study (CHS) [16] was used to operationalize baseline levels of frailty, comprising of five indicators: weight loss, exhaustion, low physical activity, slowness, and weakness. Weight loss was characterized as self-reported unintentional weight loss of 5 kg or more in the past 6 months. Exhaustion was determined based on two items from the Center for Epidemiological Studies Depression (CES-D) scale, indicating a lack of energy and poor endurance. The lowest quintile of the gender-specific total energy expended (kcal = 1.05 × metabolic equivalents [MET] × frequency × duration × body weight) was defined as low physical activity. Slowness was assessed by a 2.5-m usual walking speed test, and defined as the slowest 20% on the timed performance (m/s) of the gender-by-height categories. Grip strength was assessed using a hand dynamometer (Tanita, No. 6103, Japan), measured twice for each hand with the arm at a 90° angle and the elbow by the side of the body, and the highest value was selected. Weakness was defined as the lowest quintile of grip strength, after adjusting for gender and body mass index (BMI). Frailty status was categorized as nonfrail (0), prefrail (1–2), and frail (3–5), assigned using the number of frailty criteria met.

Cognitive impairment was defined as scoring more than 1.5 standard deviations below the age-, gender-, and education-specific norm of the Korean version of the Mini-Mental State Examination (MMSE-KC) [17]. A variable was created that combined frailty status (3 categories) and cognitive status (2 categories) into paired groups. These matched pairs consisted of 6 categories, with the nonfrail and cognitively not impaired subjects serving as the reference group.

Deaths were confirmed through interviews with the surviving spouse or next of kin during the follow-up survey conducted in 2011. The longest follow-up before censoring was 3.4 years. The month and year of death was recorded for each decedent.

The covariates considered were sociodemographics, health behaviors, and chronic conditions, from the self-reported questionnaire. Sociodemographic characteristics included age, gender, marital status (not married vs. married), education (illiterate, literate, elementary school, middle/high school, college or higher), and household income (quartiles of total annual household income divided by the square root of household size). Smoking was categorized as never, former, or current smoker. Alcohol drinking was classified as abstinent, moderate (up to 7 drinks/week for women and 14 drinks/week for men), or heavy (more than the moderate level). Self-rated health was dichotomized as good (very good, good, average) versus poor (poor, very poor). Participants were also asked about physician-diagnosed chronic conditions (hypertension, stroke, angina, diabetes mellitus, arthritis, chronic bronchitis/emphysema, asthma, cancer, chronic renal failure, fracture), with comorbidity being grouped into 0, 1, and ≥2. Depressive symptoms were determined using the Geriatric Depression Scale, short-form (GDS-15) [18], with a score of ≥8 denoting its presence.

2.3. Statistical analysis

The distribution of sample characteristics by frailty and follow-up status was analyzed with chi-square tests and analysis of variance. A Cox proportional hazards model was used to assess the risk of 3-year mortality by frailty and cognitive impairment. No significant violation of the non-proportionality assumption, based on the log-minus-log survival plots and the Schoenfeld test (p = 0.07), was revealed. A product term between frailty and cognitive impairment was included in the model to test the interaction effect on mortality. Kaplan–Meier survival curves were constructed by grouped pairs of frailty and cognitive status. Hazard ratios of mortality for the different pairs were analyzed, with the nonfrail and cognitively not impaired group serving as the reference category, adjusting for covariates (age, gender, marital status, education, household income, smoking, alcohol drinking, self-rated health, comorbidity, and depressive symptoms). Covariates were selected based on their clinical significance and p values less than 0.2 in their association with both frailty and mortality. Subgroup analyses by cognitive status were performed to examine the strength of the frailty-mortality relationship between those cognitively impaired and not impaired. In supplemental analyses, we examined the individual components of frailty and their association with mortality.

Sensitivity analyses were conducted to examine the effect of possible selection bias due to loss to follow-up on the outcome estimate. Several assumptions were tested, including the best-case scenario where none of the participants lost to follow-up were assumed to have died. More plausible worst-case scenarios evaluated mortality rates being higher in those lost to follow-up than among those followed up by a ratio of 1, 1.5, 2, and 3 [19].

All statistical tests were two-sided with a 0.05 significance level. All analyses were performed in Stata 13.1 (StataCorp, College Station, TX), incorporating sampling weights, stratification, and clustering for the complex survey design.