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Frailty as a Novel Predictor of Mortality and Hospitalization in Hemodialysis Patients of All Ages

Mara A. McAdams-DeMarco, PhD[1],[2], **Andrew Law, ScM**[1],[2], **Megan L. Salter, PhD**[1],[2], **Brian Boyarsky, BA**[1], **Luis Gimenez, MD**[3],[4],[5], **Bernard G. Jaar, MD, MPH**[2],[3],[4],[5], **Jeremy D. Walston, MD**[6], and **Dorry L. Segev, MD, PhD**[1],[2]

[1]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD

[3]Nephrology Center of Maryland, Baltimore, MD

[4]Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD

[5]Dialysis Program, Good Samaritan Hospital, Baltimore, MD

[6]Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Objectives—To quantify the prevalence of frailty in adult patients of all ages undergoing chronic hemodialysis, its relationship to comorbidity and disability, and its association with adverse outcomes of mortality and hospitalization.

Design—Prospective cohort study.

Setting—Single hemodialysis center in Baltimore, Maryland.

Participants—146 prevalent hemodialysis patients enrolled between January 2009 and March 2010 and followed through August 2012.

Measurements—Frailty, comorbidity, and disability on enrollment into the study and subsequent mortality and hospitalizations.

Results—At enrollment, 50.0% of older (age≥65) and 35.4% of younger (age<65) hemodialysis patients were frail; 35.9% and 29.3% were intermediately frail, respectively. The 3-year mortality was 16.2% for non frail, 34.4% for intermediately frail, and 40.2% for frail participants. Intermediate frailty and frailty were associated with a 2.68-fold (95% CI: 1.02-7.07, *P*=0.046) and 2.60-fold (95%CI: 1.04-6.49, *P*=0.041) higher risk of death independent of age, sex, comorbidity, and disability. In the year after enrollment, median number of hospitalizations was 1 (IQR 0-3). The proportion with 2 or more hospitalizations was 28.2% for non frail, 25.5% for intermediately frail, and 42.6% for frail participants. While intermediate frailty was not associated with the number of hospitalizations (RR=0.76, 95%CI:0.49-1.16, *P*=0.21), frailty was associated with a

Corresponding Author: Dorry Segev, M.D., Ph.D., Director of Clinical Research, Transplant Surgery, Johns Hopkins Medical Institutions, 720 Rutland Ave, Ross 771B, Baltimore, MD 21205, 410-502-6115 (tel) 410-614-2079 (fax) dorry@jhmi.edu. Alternate Corresponding Author: mmcadams@jhsph.edu.

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1.43-fold (95%CI:1.00-2.03, *P*=0.049) higher number of hospitalizations independent of age, sex, comorbidity, and disability. The association of frailty with mortality and hospitalizations did not differ between older and younger participants (Interaction *P*=0.64 and *P*=0.14, respectively).

Conclusions—Adults of all ages undergoing hemodialysis have a very high prevalence of frailty, more than 5-fold higher than community dwelling older adults. In this population, regardless of age, frailtyis a strong, independent predictor of mortality and number of hospitalizations.

Keywords

Frailty; hemodialysis; mortality; hospitalization

INTRODUCTION

Frailty is a state of decreased physiological reserve and multi-system dysregulation associated with increased vulnerability to stressors.[1]Frailty was described, and has been predominantly studied, in older adults, where it has been classified as a clinical phenotype and risk predictor independent of comorbidity and disability. In community dwelling older adults, the prevalence of frailty is 7%.[1] Frail older adults, regardless of their comorbidity and disability status, are at twice the risk of mortality and hospitalization,[1-5]as well as other adverse outcomes including falls, decreased mobility, physical limitations, respiratory impairment, and cognitive decline.[1,6-9]

There are over 500,000 patients with end-stage renal disease (ESRD) undergoing hemodialysis, of whom over half are over the age of 65; this population is at high risk of mortality as well as hospitalization, an important measure of morbidity that leads to poor outcomes and results in one-third of total ESRD expenditures.[10] Accurate risk prediction in ESRD could lead to better patient education, resource allocation, and targeted interventions. However, there is currently limited ability to predict hospitalization and mortality in this population.[11-14]While comorbidity and disability are associated with mortality and hospitalization in ESRD,[15-18] the high prevalence of these risk factors limits their ability to inform risk prediction.[19-24]Metrics of aging, like frailty, may be better suited for prediction of mortality and hospitalization than traditional risk factors, because these patients are thought to experience a physiologic decline similar to that seen in aging. Similar associations have been described in HIV,[25,26] a chronic condition that, like ESRD, is also characterized by physiologic changes resembling aging.[27-31]

For these reasons, we hypothesized that frailty, as described and validated in older adults, might be applicable to ESRD patients of all ages. The primary goals of this study were to quantify the prevalence of frailty and explore the relationship of frailty as a domain independent of comorbidity and disability in a prospective cohort of patients undergoing chronic hemodialysis.

METHODS

Study Design

This was a prospective study of prevalent hemodialysis patients from a single dialysis center in Baltimore, Maryland, recruited between January 2009 and March 2010. The Johns Hopkins Institutional Review Board approved the study. At enrollment, a trained research assistant collected medical information including date of birth, gender, race, education, tobacco use, time on hemodialysis, and comorbidities from participant interviews and medical record review. Frailty and disability were also directly measured at this time as described below.

Frailty

The main exposure of interest was frailty as defined and validated by Fried et al.[1,32-41] At enrollment, the 5 components of this frailty scale were measured: shrinking (self-report of unintentional weight loss of more than 10 lbs in the past year based on dry weight); weakness (grip-strength below an established cutoff based on gender and BMI);[1] exhaustion (self-report); low activity (Kcals/week below an established cutoff);[1] and slowed walking speed (walking time of 15 feet below an established cutoff by gender and height).[1] A score of 1 was given to those with the presence of each measured component. The aggregate frailty score was calculated as the sum of the component scores (range 0-5) and empirically categorized as nonfrail (0-1), intermediately frail (2), and frail (3-5). This categorization maintained Fried's definition of frailty, but expanded the definition of nonfrail to include a score of 1; this empiric decision was important because very few (7%) participants had a frailty score of 0.

Comorbidity

Comorbidity was defined as 4 or more of the conditions considered in Fried's landmark frailty study:[1] peripheral vascular disease (PVD), rheumatoid arthritis (RA), cancer, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, congestive heart failure (CHF), angina, and myocardial infarction (MI). All comorbidities were abstracted from the medical charts.

Disability

Activities of daily living (ADL)were measured at enrollment as previously published.[42] Participants reported the need for assistance with each of the 6ADL domains at enrollment (feeding, dressing, ambulation, grooming, using a toilet, and bathing). Disability was defined as the inability to perform at least 2 of the domains without assistance.

Outcomes

Participants were followed until August 31, 2012. Vital status and date of death (where applicable) were obtained from the dialysis center; deaths were augmented by linkage to the National Death Index. Hospitalizations in the year after enrollment were ascertained from the dialysis center as well as medical record review.

Statistical Analysis

Cox proportional hazards models were used to estimate the association between frailty and mortality. Participants were censored at kidney transplantation or end of study. Proportional hazards assumptions were confirmed by visual inspection of the complimentary log-log plots. Poisson regression models were used to estimate the association between frailty and the number of hospitalizations in 1 year. The final models for mortality and number of hospitalization were adjusted for age, sex, comorbidity, and disability. Weighted survival analysis was performed to weight each participant in our regression model by their relative representation in the US dialysis population as a whole. All analyses were performed using STATA 12.1/SE (College Station, Texas).

RESULTS

Study Population

Among 146 study participants, the mean age was 60.6 years ± 13.6, 43.8% were older adults (age≥65), 46.6% were female, and 84.3% were African American. The median follow-up time was 3.0 years (IQR: 2.4-3.1 and range: 0.2-3.2 years). Comorbidity (more than 4

conditions specified in the methods) and disability were observed in 28.8% and 19.2% of participants.

Frailty

At enrollment, 26.0% were nonfrail, 32.2% were intermediately frail, and 41.8% were frail (Figure 1). Participants who were frail and those who were intermediately frail were more likely to be older (62.9 and 62.1 vs. 55.1 years, *P*=0.01) compared to nonfrail participants (Table 1). However, both intermediate frailty and frailty were present in a high proportion of younger (29.3% and 35.4% in those under 65) as well as older (35.9% and 50.0% in those 65 or older) participants. Consistent with other populations, there was overlap between comorbidity, disability, and frailty (Figure 2): 20.5% were frail without comorbidity or disability, 10.3% were frail withcomorbidity but no disability, and 5.5% were frail with disability but no comorbidity.

Mortality

The mortality rate was58 per 1000 person-years for those who were nonfrail, 154 per 1000 person-years for those who were intermediately frail (*P*=0.03), and 163 per 1000 person-years for those who were frail (*P*=0.02). Similarly, 3-year mortality was 16.2% for nonfrail, 34.4% for intermediately frail (p=0.03), and 40.2% for frail (p=0.02) (Figure 3). Adjusting for age, sex, comorbidity, and disability, intermediate frailty was independently associated with a 2.68-fold (95% CI: 1.02-7.07, *P*=0.046) higher risk of death and frailty was associated with a 2.60-fold (95% CI: 1.04-6.49, *P*=0.041) higher risk of death(Table 2); this relationship was not modified by age (interaction between age and frailty: HR=1.07, 95% CI: 0.61-1.88, *P*=0.64). The association did not differ after adjusting for time on dialysis (Intermediately Frail: HR=2.65, 95% CI: 1.05-6.67; Frail: HR=2.87, 95% CI: 1.17-7.03) or access type (Intermediately Frail: HR=2.67, 95% CI: 1.06-6.73; Frail: HR=2.78, 95% CI: 1.12-6.88). Furthermore, the association was similar after reweighting the cohort to represent the national dialysis population (Intermediately Frail: HR=2.99, 95% CI: 1.04-8.57; Frail: HR=2.75, 95% CI: 1.04-7.27).

Hospitalization

In the year after enrollment, 51.7% of participants had 1 or more hospitalizations, 33.3% had 2 or more hospitalizations, and median (IQR) number of hospitalizations was 1 (0-3); the maximum number of hospitalizations was 9. The proportion with 1 or more hospitalizations was 46.2% for nonfrail, 44.7% for intermediately frail, and 60.7% for frail patients; similarly, proportion with 2 or more hospitalizations was 28.2% for non frail, 25.5% for intermediately frail, and 42.6% for frail participants (p=0.20 for intermediately frail and p=0.02 for frail). Adjusting for age, sex, comorbidity, and disability, intermediate frailty was not associated with number of hospitalizations (RR=0.76, 95% CI: 0.49-1.16, *P*=0.21) but frailty was associated with a 1.43-fold (95% CI: 1.00-2.03, *P*=0.049) higher number of hospitalizations (Table 2);this relationship was not modified by age (interaction between age and frailty: RR=0.81, 95% CI: 0.62-1.07, *P*=0.14). The association did not differ after adjusting for time on dialysis (Intermediately Frail: RR=0.74, 95% CI: 0.49-1.11; Frail: RR=1.47, 95% CI: 1.05-2.06) or access type (Intermediately Frail: RR=0.74, 95% CI: 0.49, 1.12; Frail: RR=1.44, 95% CI: 1.02, 2.03).

DISCUSSION

In this prospective study of adults undergoing hemodialysis, frailty had a prevalence of 41.8% and was associated with a 2.60-foldhigher risk of mortality (95% CI: 1.04-6.49, *P*=0.041) and 1.43-fold higher number of hospitalizations (95% CI: 1.00-2.03, *P*=0.049), independent of age, sex, comorbidity, and disability. This study proposes a standardized

measure of frailty that can be applied to more than 500,000 ESRD patients, extending a construct from gerontology to a population of adults of all ages suffering from the physiologic decline resulting from a chronic condition. Additionally, the findings support the hypothesis that frailty is a domain independent of comorbidity and disability, even in this novel population.

To our knowledge, this is the first study that can directly compare frailty measured in ESRD patients with the same measure of frailty in other populations. Interestingly, the prevalence of frailty among ESRD patients in our study was much (five to seven-fold) higher than in community dwelling older adults.[1]Compared with frailty prevalence of 7% in adults aged 65 or older in the Cardiovascular Health Study, 50.0% of our study participants aged 65 or older, and also 35.4% of our study participants under 65, were frail.

Our findings are consistent with subjective approximations of physiologic decline in ESRD patients as captured in registry data based on self-reported limitation in activities, self-reported fatigue, and administratively coded cachexia.[43,44] In the United States Renal Data System (USRDS) Wave 2, mortality risk for hemodialysis initiates was a 2.24-fold (95% CI 1.60-3.15) higher risk in those with physiologic decline approximated using the registry data.[44]Additionally, physiologic decline was associated with a 1.26-fold (95% CI 1.09-1.45) higher risk of hospitalization in the USRDS Comprehensive Dialysis Study (CDS) using a similar approximation.[43] However, these studies were limited by their retrospective study design, use of data not designed for studying physiologic decline, limited ability to adjust for comorbidity, inability to adjust for disability, and the absence of objective measures of frailty including weakness, weight loss, and slowed walking speed.

Strengths of this study include prospective measurement of a validated, objective construct of frailty, granular ascertainment of comorbidities using medical records abstraction, and use of a validated measure of disability. The main limitation was the prevalent sampling strategy; in other words, presence or absence of frailty was not established prior to hemodialysis initiation. As such, survivor bias limits inferences from our finding that frailty was not associated with time on hemodialysis. Our study also has the limitations inherent in a single-center study of 146 participants, both in terms of generalizability and statistical power to detect subtle subgroup effects.

This study is the first evidence of the frailty phenotype as defined by Fried *et al* in patients undergoing hemodialysis and thus, there may be concerns that not all components of frailty were contributing to the mortality effect. However, we performed analyses to assess whether frailty was truly a syndrome in adults undergoing hemodialysis. We observed that 1) the variance inflation factor was approximately 1 for all components, suggesting that there is no co linearity between the components, and 2) Akaike's Information Criterion of the full frailty phenotype (a measure of goodness-of-fit) was better than the individual components. In adults undergoing hemodialysis, frailty is a syndrome that is consistent with the phenotype Fried documented in older adults.

In this first study of a validated construct of frailty prospectively measured in ESRD patients, frailty was highly prevalent and associated with mortality and hospitalization, independent of comorbidity and disability, in adults of all ages. This finding has important implications for researchers, patients and providers in the ESRD field, potentially improving counseling, clinical decision-making, and even targeting at-risk individuals for targeted interventions. Furthermore, our findings illustrate that metrics derived from gerontology can be both prevalent and predictive of adverse outcomes in non-geriatric patients with chronic conditions such as ESRD, regardless of their age, comorbidity, or disability status.

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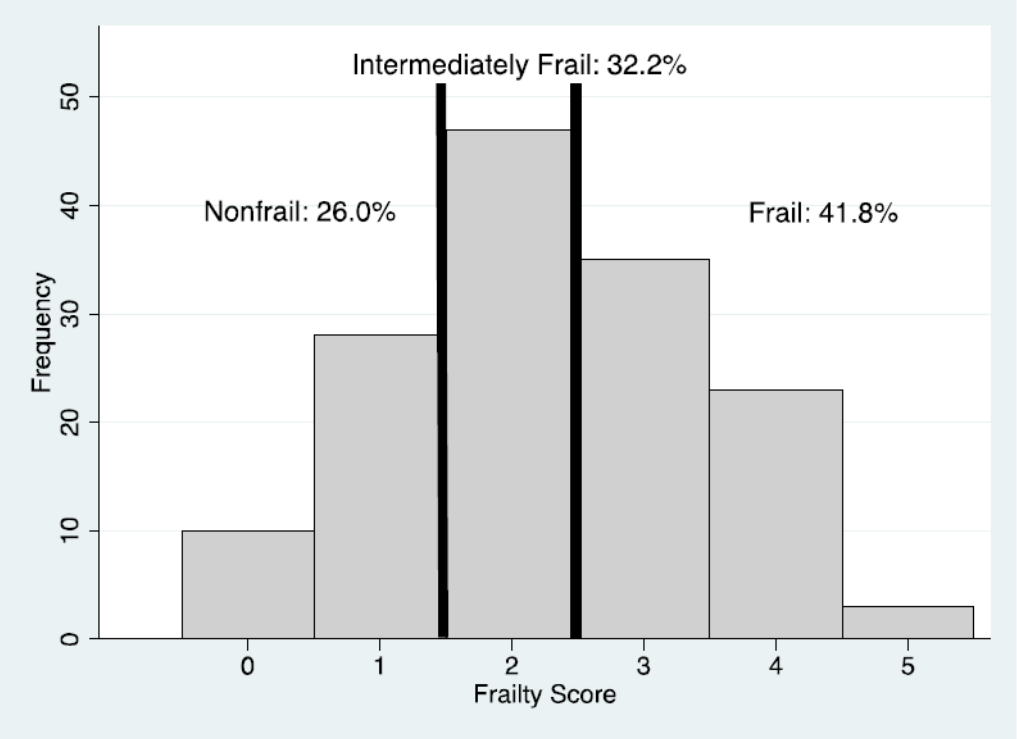

Figure 1. Distribution of Frailty Score in Study Population

The percentage of nonfrail, intermediately frail, and frail participants are listed above the cutoffs.

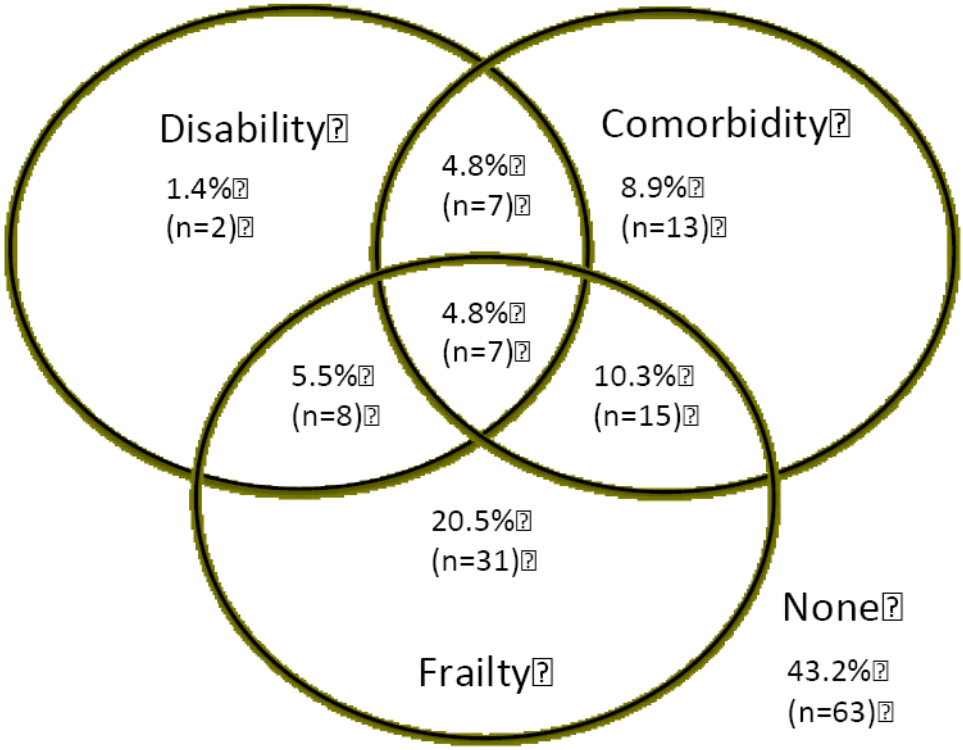

Figure 2. Overlap of Frailty, Comorbidity, and Disability

Frailty is defined as 3 or more components as defined by Fried. Disability is defined as the need for assistance in 2 or more activities of daily living categories. Comorbidity is defined as 4 or more conditions as specified in the methods. The total represents 166 study participants on hemodialysis. The *n* of each subgroup indicated in parentheses.

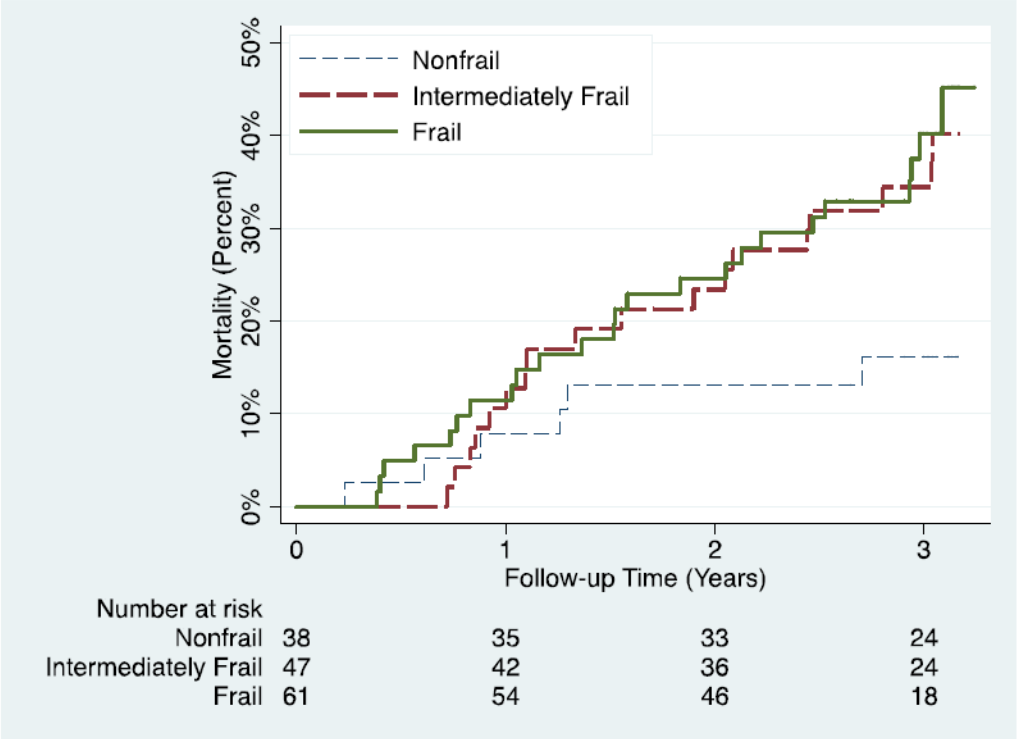

Figure 3. Estimated Cumulative Incidence of Mortality, by Frailty

Kaplan-Meier method was used to estimate curves; the log-rank test was statistically significant (*P*=0.047).

Table 1

Characteristics of Study Population, by Frailty

	Nonfrail (n=38)	Intermediately Frail (n=47)	Frail (n=61)	*P* value
Female sex	42.1	40.4	54.1	0.30
Age	55.1 ± 13.4	62.1 ± 13.7	62.9 ± 12.9	0.01
Black race	89.5	85.1	80.3	0.50
Enrollment body mass index (kg/m^2)	28.9 ±8.8	28.4 ± 7.8	28.7 ± 7.8	0.97
Pre-dialysis body mass index (kg/m^2)	28.6 ± 8.9	29.3 ± 8.6	31.6±9.6	0.23
Tobacco use (history of smoking)	15.8	19.2	26.2	0.49
Time on hemodialysis (years)*	4.5 [4.4]	3.7 [4.4]	3.3 [5.3]	0.78
High school or higher education Comorbidities	79.0	85.1	80.3	0.74
Peripheral vascular disease	10.5	29.8	42.6	0.002
Rheumatoid arthritis	5.3	6.4	8.2	0.92
History of cancer	15.8	23.4	16.4	0.59
Hypertension	94.7	85.1	88.5	0.37
Chronic obstructive pulmonary disease	7.9	23.4	23.0	0.12
Diabetes	44.7	70.2	75.4	0.01
Congestive heart failure	47.4	34.0	37.7	0.45
Angina	7.9	4.3	3.3	0.55
Myocardial infarction	18.4	10.6	19.7	0.44
Number of comorbidities	2.4 ±1.3	2.8 ± 1.5	3.0 ±1.5	0.13
Comorbidity**	15.8	29.8	36.1	0.09
Disability**	15.8	12.8	26.2	0.19

Mean ±standard deviations are reported for continuous variables.

* Median and interquartile range provided.

** As defined by Fried et al;[1] see methods.

Table 2

Mortality and Hospitalization, by Frailty

	Nonfrail	Intermediately Frail	Frail
Hazard ratio of Mortality			
Unadjusted	Reference	2.67 (1.06, 6.73)	2.90 (1.18, 7.11)
Adjusted for age, sex, comorbidity, and disability	Reference	2.68 (1.02, 7.07)	2.60 (1.04, 6.49)
Incident Rate Ratio of Hospitalization			
Unadjusted	Reference	0.74 (0.49, 1.12)	1.48 (1.05, 2.07)
Adjusted for age, sex, comorbidity, and disability	Reference	0.76 (0.49, 1.16)	1.43 (1.00, 2.03)