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The Relationship Between Intervening Hospitalizations and Transitions Between Frailty States

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Background. Frailty among older persons is a dynamic process, characterized by frequent transitions between frailty states over time. We performed a prospective longitudinal study to evaluate the relationship between intervening hospitalizations and these transitions.

Methods. We studied 754 nondisabled community-living persons, aged 70 years or older. Frailty, assessed every 18 months for 108 months, was defined on the basis of muscle weakness, exhaustion, low physical activity, shrinking, and slow walking speed. Participants were classified as frail if they met three or more of these criteria, prefrail if they met one or two of the criteria, or nonfrail if they met none of the criteria. Hospitalizations were ascertained every month for a median of 108 months.

Results. The exposure rates (95% confidence interval) of hospitalization per 1,000 months, based on frailty status at the start of each 18-month interval, were 19.7 (16.2–24.0) nonfrail, 32.9 (29.8–36.2) prefrail, and 57.2 (52.9–63.1) frail. The likelihood of transitioning from states of greater frailty to lesser frailty (ie, recovering) was consistently lower based on exposure to intervening hospitalizations, with adjusted hazard ratios per each hospitalization ranging from 0.46 (95% confidence interval: 0.21–1.03) for the transition from frail to nonfrail states to 0.52 (95% confidence interval: 0.42–0.65) for the transition from prefrail to nonfrail states. Hospitalization had more modest and less consistent effects on transitions from states of lesser frailty to greater frailty. Nonetheless, transitions from nonfrail to frail states were uncommon in the absence of a hospitalization.

Conclusions. Recovery from prefrail and frail states is substantially diminished by intervening hospitalizations. These results provide additional evidence highlighting the adverse consequences of hospitalization in older persons.

Key Words: Frailty—Hospitalization—Longitudinal study.

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INCREASINGLY, frailty is recognized as a geriatric syndrome, distinct from disability and comorbidity, which results from a multisystem reduction in reserve capacity, confers high risk for an array of adverse outcomes, and is potentially amenable to prevention and remediation (1–3). As an indicator of its societal importance, the Institute of Medicine has identified frailty as one of 20 priority areas (selected from several hundred potential candidates) in need for improvement in health care quality (4).

In prior work, we have demonstrated that frailty is a dynamic process, characterized by frequent transitions between frailty states (nonfrail, prefrail, and frail) over time (5). These findings have since been confirmed by other investigators (6). The reasons behind these transitions are largely unknown, although numerous studies have evaluated potential risk factors for the initial onset of frailty (7–11). One possibility is that transitions between frailty states are driven, at least in part, by intervening illnesses and injuries leading to hospitalization. These intervening hospitalizations, for example, could impede recovery from states of greater frailty to lesser frailty and, in turn, place older persons at higher risk for subsequent adverse outcomes. In support of this possibility, we have recently shown that hospitalization in older persons has pronounced deleterious effects on nearly all transitions between states of disability over the course of more than 10 years (12).

To improve our understanding of frailty among older persons, we set out in the current study to determine the relationship between intervening hospitalizations and transitions between frailty states over time. We hypothesized that transitions from nonfrail to frail would be uncommon in the absence of a hospitalization and that intervening illnesses and injuries leading to hospitalization would reduce the likelihood of transitioning from states of greater frailty to states of lesser frailty (ie, impede recovery).

Methods

Study Population

Participants were members of the Precipitating Events Project, a longitudinal study of 754 community-living persons,

aged 70 years or older, who were nondisabled (ie, required no personal assistance) at baseline in four essential activities of daily living—bathing, dressing, walking inside the house, and transferring from a chair (13). Exclusion criteria included significant cognitive impairment with no available proxy (14), inability to speak English, diagnosis of a terminal illness with a life expectancy less than 12 months, and a plan to move out of the New Haven area during the next 12 months.

The assembly of the cohort, which took place between March 1998 and October 1999, has been described in detail elsewhere (13,15). In brief, potential participants were identified from a computerized list of 3,157 age-eligible members of a large health plan in greater New Haven, Connecticut. Based on our initial sample size calculations, persons with slow gait speed (ie, require >10 seconds to walk back and forth over a 10-ft [3-m] course as quickly as possible) were oversampled. Eligibility was determined during a screening telephone interview and was confirmed during an in-home assessment. Only 4.6% of the 2,753 health plan members who were alive and could be contacted refused to complete the screening telephone interview, and 75.2% of the eligible members agreed to participate in the project. Persons who refused to participate did not differ significantly from those who were enrolled in terms of age or sex. The study protocol was approved by the Yale Human Investigation Committee, and all participants provided verbal informed consent.

Data Collection

Comprehensive home-based assessments were completed at baseline and subsequently at 18-month intervals for 108 months, whereas telephone interviews were completed monthly up to September 2008, with a completion rate greater than 99%. For participants with significant cognitive impairment, the monthly interviews and relevant parts of the comprehensive assessments were completed with a designated proxy. Based on a substudy in which 20 cognitively intact participants and their designated proxies were interviewed separately for six consecutive months, we found that the accuracy of these proxy reports was high, with $\kappa = 1.0$ for hospitalization (12). Deaths were ascertained by review of the local obituaries and/or from an informant during a subsequent telephone interview. Attrition for reasons other than death was less than 5%.

Assessment of frailty.—Data from the comprehensive assessments were used to define each of the five criteria for frailty: muscle weakness, exhaustion, low physical activity, shrinking, and slow walking speed. As described previously (5), our operational definitions for the last three criteria differed modestly from those previously described by Fried and colleagues (16) for use in the Cardiovascular Health Study . The physical activity criterion was met for men who scored less than 64 and women who scored less than 52 on the Physical Activity Scale for the Elderly (17). The shrinking criterion was met if the participant answered "Yes" when asked, "In the past year, have you lost more than 10 pounds?" or (given the extended follow-up period) if the body mass index was less than 18.5 kg/m^2 (18). Finally, the slow walking speed criterion was met if the participant scored greater than 10 seconds on the rapid gait test (13). These modified criteria have strong predictive validity (19).

Participants were classified as frail if they met three or more of the aforementioned criteria, as prefrail if they met one or two of the criteria, or as nonfrail if they met none of the criteria. Among a subgroup of 24 participants who were evaluated independently within a 3-day period by different nurse researchers, we found that the reliability of our frailty assessment was substantial (20), with a weighted $\kappa = .78$. To address the small amount of missing data on frailty, which ranged from 0.3% at baseline to 2.5% at 90 months, we performed multiple imputation with 50 random draws per missing observation using procedures described in an earlier report (21).

Frailty transitions.—Transitions in frailty were evaluated for each of the 18-month intervals. Nine transitions were possible—six among the three frailty states and one from each of the frailty states to death.

Assessment of covariates.—During each of the comprehensive assessments, data were collected on several covariates, including demographic characteristics, cognitive status as assessed by the Folstein Mini-Mental State Examination (22), and nine self-reported, physician-diagnosed chronic conditions: hypertension, myocardial infarction, congestive heart failure, stroke, diabetes mellitus, arthritis, hip fracture, chronic lung disease, and cancer. Data on these covariates were 100% complete at baseline and greater than 95% complete during the subsequent comprehensive assessments. Participants were considered to be cognitively impaired if they scored less than 24 on the Mini-Mental State Examination (22).

Assessment of hospitalization.—During the monthly telephone interviews, participants were asked whether they had stayed at least overnight in a hospital since the last interview, that is, during the past month. The accuracy of these reports, based on an independent review of hospital records among a subgroup of 94 participants, was high, with $\kappa = 0.94$ (23). For participants who had died, a final interview was completed with a proxy informant who was asked about any hospitalizations since the prior interview.

Statistical Analysis

Sixteen (2.1%) members of the cohort dropped out of the study before the first follow-up assessment at 18 months, leaving 738 participants in the analytic sample. To quantify

Table 1. Rates of Frailty Transitions per 1,000 Person-Months According to Hospitalization During Relevant 18-Month Intervals*

Transition†	Overall	One or More Hospitalizations	No Hospitalizations	*p* Value
Nonfrail to				
Prefrail	22.1 (19.7–24.8)	25.1 (21.0–30.1)	21.2 (18.5–24.3)	.144
Frail	2.8 (1.9–4.0)	5.6 (3.5–9.1)	1.9 (1.2–3.2)	.012
Death	1.3 (0.8–2.2)	4.1 (2.3–7.3)	0.5 (0.2–1.2)	.003
Prefrail to				
Nonfrail	6.2 (5.3–7.2)	4.3 (3.2–5.7)	7.2 (6.1–8.6)	<.001
Frail	15.4 (14.1–16.8)	20.6 (18.4–23.0)	12.5 (11.1–14.1)	<.001
Death	2.7 (2.2–3.4)	6.2 (4.8–7.9)	0.9 (0.5–1.4)	<.001
Frail to				
Nonfrail	0.3 (0.1–0.6)	0.2 (0.1–0.8)	0.3 (0.1–0.9)	.477
Prefrail	9.1 (7.8–10.5)	4.8 (3.7–6.3)	12.9 (11.0–15.2)	<.001
Death	11.0 (9.8–12.4)	18.4 (16.1–20.9)	4.3 (3.3–5.7)	<.001

Notes: *Frailty transitions were evaluated every 18 months, and exposure to hospitalizations was determined during the 18-month interval corresponding to the specific transition. Point estimates are accompanied by 95% confidence intervals as described in the "Methods."

†The number (%) of participants without a transition during the entire follow-up period was 16 (9.5%), 31 (8.3%), and 32 (16.3%), respectively, for participants who were nonfrail, prefrail, and frail.

exposure to hospitalization, we calculated the mean rate as the number of person-months hospitalized over all person-months observed. We report these rates per 1,000 months according to frailty status at the start of each 18-month interval. Next, we calculated rates for each of the frailty transitions per 1,000 person-months over the entire follow-up period, and we report these rates according to the presence or absence of any hospital admission during the 18-month interval corresponding to the specific transition. Generalized estimating equations Poisson models were used to determine CIs for the exposure rates and transition rates and to calculate *p* values for the comparison of transition rates according to exposure to any hospitalization.

To evaluate the multivariable relationships between hospitalization and nine frailty transitions, we used a competing risk Cox model for recurrent events (24). In this model, persons are simultaneously at risk for several "competing" outcomes. For example, participants who were prefrail were at risk for transitions to nonfrail, frail, and death. The model calculates the respective associations based on the amount of time participants spend in a specific state prior to transitioning to another state. The competing risk Cox model accounts for the correlation among observations within individuals through the use of robust sandwich variance estimators for standard errors of the coefficients (25) and can be used for nonproportional hazards, which may occur with time-dependent variables (26). The calculated hazard ratio refers to the marginal risk of making a specific transition based on exposure to each additional hospitalization over an 18-month interval.

The multivariable models included three fixed covariates—sex, race/ethnicity, and years of education—and four time-varying covariates—age 85 years or older, living alone, number of chronic conditions, and cognitive impairment. These covariates represent important sociodemographic factors and pertinent clinical factors. The time-varying covariates were updated using data from the comprehensive assessment at the start of each 18-month interval. The results did not change when baseline frailty was included as a fixed covariate. All statistical tests were two tailed, and all analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

At baseline, the mean (standard deviation) age of participants in our analytic sample was 78.4 (5.3) years. Of the 738 participants, 476 (64.5%) were women, 667 (90.4%) were non-Hispanic white, 291 (39.4%) lived alone, and 83 (11.3%) were cognitively impaired. On average, participants had 12.0 (2.9) years of education and 1.8 (1.2) chronic conditions. The distribution of participants according to baseline frailty status was 169 (22.9%) nonfrail, 373 (51.5%) prefrail, and 196 (26.6%) frail.

During a median follow-up of 108 months, 660 (89.4%) of the participants had at least one hospitalization, and 651 (88.0%) had at least one frailty transition. Of the 3,535 18-month intervals, 754 (21.3%) included a single hospitalization, whereas 709 (17.2%) included two or more hospitalizations. These hospitalizations were distributed fairly equally over the 18-month intervals. The exposure rates (95% confidence interval) of hospitalization per 1,000 months, based on frailty status at the start of each 18-month interval, were 19.7 (16.2–24.0) nonfrail, 32.9 (29.8–36.2) prefrail, and 57.2 (52.9–63.1) frail. Table 1 provides information on the rates of frailty transitions during the 18-month intervals. Overall, transitions were observed most commonly from nonfrail to prefrail states and least commonly from frail to nonfrail states. Without exception, the transition rates to states representing worsening frailty were higher in the presence of hospitalization than in the absence of hospitalization, whereas the opposite was true for transitions representing a reduction in frailty, although these differences were not statistically significant for the transition

Table 2. Multivariable Associations Between Hospitalization and Frailty Transitions Over 18-Month Intervals*

Transition	HR (95% CI)	*p* Value
Nonfrail to		
Prefrail	0.94 (0.79–1.11)	.461
Frail	1.33 (1.06–1.66)	.015
Death	1.64 (1.25–2.16)	<.001
Prefrail to		
Nonfrail	0.52 (0.42–0.65)	<.001
Frail	1.07 (1.00–1.15)	.060
Death	1.45 (1.31–1.61)	<.001
Frail to		
Nonfrail	0.46 (0.21–1.03)	.058
Prefrail	0.48 (0.40–0.58)	<.001
Death	1.29 (1.20–1.39)	<.001

Notes: CI = confidence interval; HR = hazard ratio.

*As described in the "Methods," a single multivariable model was run that included three fixed covariates—sex, race/ethnicity, and years of education, and four time-dependent covariates—age 85 years or older, living alone, number of chronic conditions, and cognitive impairment. The time-dependent covariates were updated every 18 months during the comprehensive assessments. The hazard ratio refers to the marginal risk of making a specific transition based on exposure to each additional hospitalization over an 18-month interval.

from nonfrail to prefrail and from frail to nonfrail. Transitions from nonfrail to frail were particularly uncommon in the absence of a hospitalization, with a rate of 1.9 (confidence interval: 1.2–3.2) per 1,000 person-months as compared with a rate of 5.6 (3.5–9.1) per 1,000 person-months in the presence of a hospitalization. For each of the frailty states, the transition rate to death was substantially higher during intervals with at least one hospitalization than those without a hospitalization.

The multivariable associations between hospitalization and the frailty transitions are shown in Table 2. Hospitalization was not associated with the transition from nonfrail to prefrail states but was significantly associated with the transition from nonfrail to frail states (with a 33% increase in risk for each hospitalization) and marginally associated with the transition from prefrail to frail states. In contrast, the likelihood of transitioning from states of greater frailty to lesser frailty (ie, recovering) was consistently lower based on exposure to hospitalization, with adjusted hazard ratios per each hospitalization ranging from 0.46 (marginal *p* value of .058) for the transition from frail to nonfrail states to 0.52 ($p < .001$) for the transtion from prefrail to nonfrail states. Similarly, hospitalization was strongly associated with the transition to death from each of the three frailty states, with adjusted hazard ratios per each hospitalization as high as 1.64 for the transition from nonfrail to death.

Discussion

In this prospective, longitudinal study of older men and women, we found that illnesses and injuries leading to hospitalization reduced the likelihood of transitioning from states of greater frailty to lesser frailty (ie, impeded recovery) but had more modest and less consistent effects on transitions from states of lesser frailty to greater frailty. In addition, intervening hospitalizations were strongly associated with the transition to death from each of the three frailty states. These findings provide new insights into the processes underlying the development, progression, and amelioration of frailty in older persons.

For many years, the term "frailty" had been used rather loosely to describe a condition of old age that denoted debility or feebleness and that led inexorably to functional decline, disability, and death (27). During the past decade, however, the conceptual focus has sharpened, and frailty is now considered a state of increased vulnerability, resulting from a multisystem reduction in reserve capacity (1). Because reserve capacity can be boosted and not just diminished (28,29), frailty should no longer be deemed as an "absorbing" state. Indeed, increasing evidence indicates that transitions from states of greater frailty to lesser frailty are not uncommon (5,6), meaning that many older persons have the capacity to recover from frailty and prefrailty, respectively. Yet, relatively little is known about the processes underlying transitions between frailty states, despite their high rates, and to our knowledge, no prior study has evaluated the potential role of intervening hospitalizations in impeding or precipitating these transitions.

In the current study, we found that the likelihood of attaining a less frail state (ie, recovering), whether from prefrail to nonfrail or from frail to either nonfrail or prefrail, was reduced by about 50% for each intervening hospitalization. The higher rates of hospitalization observed among participants who were prefrail or frail than among those who were nonfrail enhance the clinical relevance of these findings, which are consistent with those of a recent report demonstrating that recovery from disability is impeded by an intervening hospitalization (12). These effects, however, were short term, that is, occurring over the course of a month, whereas those in the current study were long term, that is, occurring over the course of several months.

Although the deleterious effects of hospitalization on functional and cognitive status have been well established (30–35), the role of intervening hospitalizations on transitions between frailty states has not been previously evaluated, thereby heightening the importance of the current study. Because frailty is a distinct geriatric syndrome (1), prior work on functional and cognitive status may not be directly applicable. The adverse consequences of intervening hospitalizations are likely attributable to both the underlying illness or injury leading to hospitalization and the well-known hazards of hospitalization itself (36). Our findings highlight the importance of reducing preventable hospitalizations (37–40) and of managing older patients more effectively to prevent hospital-acquired complications (41–43).

As we had postulated, the likelihood of transitioning from a nonfrail to frail state was relatively low in the absence of a hospitalization. After accounting for several fixed and time-dependent covariates, the risk of this transition

increased by 33% for each hospitalization. The effect of hospitalization, however, was much less impressive for the transition from prefrail to frail states, with an adjusted hazard ratio of only 1.07, and was absent for the transition from nonfrail to prefrail states.

When interpreting the modest and inconsistent associations between hospitalization and transitions from states of lesser frailty to greater frailty, two possible explanations should be considered. First, although frailty was evaluated every 18 months, transitions that occurred over shorter periods of time may have been missed. For example, during an 18-month interval, a participant could have transitioned from nonfrail to prefrail or from prefrail to frail in the setting of an intervening hospitalization but, subsequently, could have transitioned back to their initial state, in the absence of another hospitalization, by the end of the interval. This scenario would have weakened the associations between an intervening hospitalization and transitions between states of lesser frailty to greater frailty. Second, our ability to detect a clinically meaningful and statistically significant association between the intervening hospitalizations and worsening frailty may have been diminished by the competing risk of death, which was substantially elevated among participants who were nonfrail and prefrail, respectively.

Several additional limitations should be noted. First, information was not available on the severity of the illnesses or injuries leading to hospitalization, on hospital-acquired complications, or on length of stay or posthospital course. Second, it was not possible to distinguish emergent hospitalizations from hospital admissions that were designed to be restorative, for example, total hip replacement for severe osteoarthritis. The number of restorative hospitalizations, however, is likely to be relatively small. Furthermore, we have previously shown that intervening hospitalizations, ascertained using the same set of procedures as in the current study, had a pronounced deleterious effect on nearly all transitions between states of disability (12), although these transitions were assessed at monthly rather than 18-month intervals. Third, because frailty was assessed much less frequently than hospitalization, we cannot exclude the possibility that at least some of the frailty transitions followed rather than preceded the hospitalizations. Hence, as is true for any observational study, we cannot firmly establish a cause–effect relationship between hospitalization and the frailty transitions. Our multivariable models adjusted for the most relevant factors that may have confounded these relationships.

Fourth, our assessment of frailty included modified but validated versions of the five criteria that were initially operationalized by Fried and colleagues using data from the Cardiovascular Health Study (5,16). Although these modifications may have modestly affected our point estimates of frailty, they should have had relatively little effect on the transition rates, which reflect changes in frailty over time. The high reliability of our assessment suggests that most of the observed transitions represent true changes in frailty status rather than measurement error. Given the clinical complexity of frailty, however, some investigators (44) have cautioned that it would be premature to accept the Fried and colleagues definition of frailty as the reference standard, despite strong evidence supporting its validity (6,45,46). Finally, because our study participants were members of a single health plan in a small urban area and were oversampled for slow gait speed, our results may not be generalizable to older persons in other settings. However, the demographic characteristics of our cohort did reflect those of older persons in New Haven County, Connecticut, which are similar to the characteristics of the U.S. population as a whole, with the exception of race or ethnic group (38). The generalizability of our results is enhanced by our high participation rate, which was greater than 75%.

Other important strengths of our study include the long duration of follow-up, low rate of attrition for reasons other than death, completeness of data collection, not only for the exposure variable but also for the outcome measures and covariates, and an analytic strategy that rigorously accounted for the competing risk of death.

The results of the current study provide additional evidence highlighting the adverse consequences of illnesses and injuries leading to hospitalization in older persons. These events likely contribute not only to short-term changes in functional status (12,33) but also to long-term changes that could threaten the functional independence of older persons by impeding recovery from prefrail and frail states.

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