The Association of Frailty With Post-ICU Disability, Nursing Home Admission, and Mortality

A Longitudinal Study

Lauren E. Ferrante, MD, MHS; Margaret A. Pisani, MD, MPH; Terrence E. Murphy, PhD; Evelyn A. Gahbauer, MD, MPH; Linda S. Leo-Summers, MPH; and Thomas M. Gill, MD

BACKGROUND: Frailty is a strong indicator of vulnerability among older persons, but its association with ICU outcomes has not been evaluated prospectively (ie, with objective measurements obtained prior to ICU admission). Our objective was to prospectively evaluate the relationship between frailty and post-ICU disability, incident nursing home admission, and death.

METHODS: The parent cohort included 754 adults aged ≥ 70 years, who were evaluated monthly for disability in 13 functional activities and every 18 months for frailty (1998-2014). Frailty was assessed using the Fried index, where frailty, prefrailty, and nonfrailty were defined, respectively, as at least three, one or two, and zero criteria (of five). The analytic sample included 391 ICU admissions.

RESULTS: The mean age was 84.0 years. Frailty and prefrailty were present prior to 213 (54.5%) and 140 (35.8%) of the 391 admissions, respectively. Relative to nonfrailty, frailty was associated with 41% greater disability over the 6 months following a critical illness (adjusted risk ratio, 1.41; 95% CI, 1.12-1.78); prefrailty conferred 28% greater disability (adjusted risk ratio, 1.28; 95% CI, 1.01-1.63). Frailty (odds ratio, 3.52; 95% CI, 1.23-10.08), but not prefrailty (odds ratio, 2.01; 95% CI, 0.77-5.24), was associated with increased nursing home admission. Each one-point increase in frailty count (range, 0-5) was associated with double the likelihood of death (hazard ratio, 2.00; 95% CI, 1.33-3.00) through 6 months of follow-up.

CONCLUSIONS: Pre-ICU frailty status was associated with increased post-ICU disability and new nursing home admission among ICU survivors, and death among all admissions. Pre-ICU frailty status may provide prognostic information about outcomes after a critical illness.

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ABBREVIATIONS: ADLs = activities of daily living; IADLs = instrumental activities of daily living; RR = relative risk

AFFILIATIONS: From the Section of Pulmonary, Critical Care, and Sleep Medicine (Drs Ferrante and Pisani) and the Section of Geriatrics (Drs Murphy, Gahbauer, and Gill, and Ms Leo-Summers), Department of Internal Medicine, Yale School of Medicine, New Haven, CT.

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With the aging of our population¹ and improvement in ICU survivorship, the number of older ICU survivors will continue to rise.² Older ICU survivors are disproportionately affected by disability,^{3,4} which can threaten their ability to live independently⁵; yet the majority of older adults value maintaining independence over staying alive.⁶ Although many factors can be used for risk stratification of post-ICU disability and other outcomes,^{4,7,8} consideration of pre-existing (ie, pre-ICU) vulnerability factors may help inform shared decision-making during outpatient advance care planning and in the ICU.

Frailty, a multidimensional syndrome that confers increased vulnerability to adverse outcomes, is increasingly common with advancing age.^{9,10} In population-based cohorts of older adults, frailty has been associated with falls, hospitalization, institutionalization, and death.¹¹ The most widely used frailty measure in the literature is the Fried index,¹² which requires an assessment of five criteria: unintentional weight loss, slow gait speed, low physical activity, muscle weakness, and

exhaustion.⁹ Because an objective assessment of these five criteria is often not possible at ICU admission, recent critical care studies have used the Clinical Frailty Scale, a subjective measure that combines elements of disease, frailty, and disability to retrospectively assess pre-ICU frailty status.^{13,14} To date, the association of frailty with post-ICU outcomes has not been evaluated longitudinally (ie, using objective measurements of frailty obtained prior to the ICU admission), nor has pre-ICU frailty been measured with the Fried index.

To address these gaps in the literature, we used data from a unique longitudinal study that includes repeated assessments of frailty and functional status for more than 15 years. Our prospective, longitudinal design allowed for an objective assessment of the Fried frailty criteria prior to the critical illness. Our aim was to test the hypothesis that pre-ICU frailty status is significantly associated with three outcomes: post-ICU disability over 6 months of follow-up, incident nursing home admission, and death from admission through 6 months of follow-up.

Methods

Study Population

Participants were drawn from the Precipitating Events Project (PEP), an ongoing longitudinal study of 754 community-dwelling adults aged ≥ 70 years, who were initially nondisabled in four activities of daily living (ADLs), as previously described.^{15,16} The Yale Human Investigation Committee approved the study (HIC #9707009635). All participants provided informed consent.

Data Collection

All participants underwent comprehensive home-based assessments at baseline and at 18-month intervals for 180 months. Telephone interviews were completed monthly through June 2014. For participants with significant cognitive impairment or who were unavailable, a proxy informant was interviewed.¹⁷ Deaths were ascertained by review of obituaries and/or from a proxy informant. Information on hospitalizations and nursing home admissions was obtained during the monthly interviews; additional details are provided in [e-Appendix 1](#). A total of 613 participants (81.3%) died after a median follow-up of 98 months, while 43 (5.7%) dropped out after a median follow-up of 27 months; data were otherwise available for 99.2% of 81,188 monthly interviews.

Assessment of Frailty and Covariates

During the comprehensive assessments, participants were evaluated using the Fried frailty index,⁹ as described previously¹⁸ and in [e-Appendix 1](#). Frailty, prefrailty, and nonfrailty were defined, respectively, as 3 to 5, 1 or 2, and 0 positive criteria. For descriptive purposes, this three-level

frailty variable is subsequently referred to as “Fried frailty status,” whereas the ordinal (0-5) form is referred to as “Fried frailty count.” The assessment of covariates is provided in [e-Appendix 1](#).

Assessment of Disability

During each of the monthly interviews, participants were asked, “At the present time, do you need help from another person to [complete the task]?” for each of four basic activities (bathing, dressing, walking, transferring), five instrumental activities (shopping, housework, meal preparation, taking medications, managing finances), and three mobility activities (walk one-quarter mile, climb a flight of stairs, and lift/carry 10 pounds). For these 12 activities, disability was defined as the need for personal assistance or inability to perform the task. Participants were also asked, “Have you driven a car during the past month?” To maintain consistency with the other activities, participants who responded “no” were classified as being “disabled” in driving.¹⁹ To address the small amount (0.8%) of missing disability data, we used multiple imputation with 100 random draws per missing observation.²⁰

Ascertainment of ICU Admissions and Acquisition of ICU Data

For the majority of the sample, ICU admissions were identified through critical care revenue codes using linked Medicare claims data. We included codes for general, specialty, and coronary care units, while excluding psychiatric or intermediate critical care.²¹ For participants in managed Medicare, information was first obtained on hospitalizations from the monthly interviews. To identify ICU admissions, a manual medical record review of each hospitalization was then performed, as previously described.²² For all ICU admissions, data were obtained about ICU length of stay, the need for mechanical ventilation, and the presence of shock, as described in [e-Appendix 1](#).^{16,22,23}

Assembly of the Analytic Samples and Definition of Outcomes

We considered all ICU admissions from study enrollment through December 2013 ([Fig 1](#)).²⁴ Because frailty status was updated during the comprehensive assessments, only the first ICU admission within

CORRESPONDENCE TO: Lauren E. Ferrante, MD, MHS, Section of Pulmonary, Critical Care, and Sleep Medicine, Yale School of Medicine, 300 Cedar St, TAC S-431, P.O. Box 208057, New Haven, CT 06520; e-mail: lauren.ferrante@yale.edu

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Figure 1 – Assembly of analytic samples from the parent cohort. All ICU admissions from study enrollment through December 2013 were identified. Because frailty was updated during the comprehensive assessments, only the first ICU admission per 18-month interval was included, yielding 391 eligible ICU admissions. For the primary outcome of post-ICU disability count, the analytic sample included 266 ICU admissions contributed by participants who survived to the first post-ICU monthly interview. For the secondary outcome of incident nursing home admission, the analytic sample included 267 ICU admissions contributed by participants who were community-living prior to ICU admission. For the mortality outcome, the analytic sample included all 391 ICU admissions. NH = nursing home. Reprinted with permission of the American Thoracic Society. Copyright 2018 American Thoracic Society. Ferrante LE, Murphy TE, Gahbauer EA, Leo-Summers LS, Pisani MA, Gill TM. Pre-Intensive care unit cognitive status, subsequent disability, and new nursing home admission among critically ill older adults. *Ann Am Thor Soc*. 2018; 15:622-629.²⁴ *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.

an 18-month interval was included. Overall, 391 ICU admissions were eligible for the study.

The primary outcome was the disability count (0-13) over the 6 months following an ICU stay. To reduce potential floor effects, ICU admissions (n = 48) were excluded when the disability count in the prior month was 13 (maximum). The analytic sample included 266 ICU admissions from participants who survived to the first post-ICU monthly interview. For the secondary outcome of incident nursing home admission, the analytic sample included 267 admissions from participants who were community-living prior to hospitalization and survived through hospital discharge. For the

secondary outcome of death from admission through 6 months of follow-up, all 391 admissions were evaluated.

Statistical Analysis

We determined the mean (SD) number of disabilities by frailty status over the 6 months following an ICU stay, with the disability count from the month prior to ICU admission included as a reference point. For the multivariable model, covariates were chosen a priori based on clinical relevance and prior work,^{16,22} and included age, sex, race, education, body mass index, depressive symptoms, number of chronic conditions, cognitive status, disability count from the month prior to ICU

admission, ICU length of stay, mechanical ventilation,²⁵ and shock. We used a negative binomial model with generalized estimating equations to adjust the standard error for each participant's repeated measurements. The model calculated the adjusted associations as relative risks (RRs), which represent the proportional increase in the average post-ICU disability count attributable to frailty status (ie, frailty or prefrailty), referent to nonfrailty. For descriptive purposes, we also provided the mean (SD) number of disabilities for the three subscales of disability (ADLs, instrumental activities of daily living [IADLs], and mobility activities) by frailty status.

We evaluated the secondary outcome of incident nursing home admission using a multivariable logistic regression model with the same covariates noted above. For the mortality outcome, we plotted Kaplan-Meier survival from admission through 6 months of

follow-up by frailty status, using the log-rank test to evaluate equality of survival. In the multivariable analysis, Fried frailty status had poor functional form, so the Fried frailty count (0-5) was substituted,²⁶ and interaction terms with time were added for age, pre-ICU disability count, and frailty count to account for noncompliance with the proportional hazards assumption.²⁷ We then evaluated the association between Fried frailty count and death from admission through 6 months of follow-up, using a Cox regression model with the aforementioned set of covariates.

A series of sensitivity analyses was performed to assess for potential bias due to the competing risk of death (e-Appendix 1). All analyses were performed with SAS (version 9.4; SAS Institute), and $P < .05$ (two-tailed) was used to indicate statistical significance.

Results

Frailty, prefrailty, and nonfrailty were present in 120 (45.1%), 114 (42.9%), and 32 (12.0%) of the 266

admissions contributed by ICU survivors in the primary analysis (Table 1).^{28,29} As frailty status worsened, many of the characteristics described in Table 1 increased or

TABLE 1 Characteristics of ICU Admissions From Participants Who Survived to the First Post-ICU Functional Assessment According to Pre-ICU Fried Frailty Status: N = 266^{a,b}

Characteristic	Mean $\pm$ SD or n (%)			
	Total (N = 266)	Not Frail (n = 32)	Prefrail (n = 114)	Frail (n = 120)
Age, y	83.5 $\pm$ 5.4	80.1 $\pm$ 3.8	82.6 $\pm$ 4.9	85.3 $\pm$ 5.5
Female sex	156 (58.6)	17 (53.1)	65 (57.0)	74 (61.7)
Non-Hispanic white	235 (88.3)	29 (90.6)	100 (87.7)	106 (88.3)
Education, y	12.0 $\pm$ 2.9	12.8 $\pm$ 2.4	12.1 $\pm$ 3.0	11.7 $\pm$ 2.9
Number of chronic conditions ^c	2.5 $\pm$ 1.3	2.0 $\pm$ 1.0	2.3 $\pm$ 1.3	2.7 $\pm$ 1.3
Pre-ICU disability ^d	4.6 $\pm$ 3.5	2.1 $\pm$ 2.4	3.3 $\pm$ 3.0	6.5 $\pm$ 3.2
Cognitive impairment ^e	46 (17.3)	3 (9.4)	15 (13.2)	28 (23.3)
Depressive symptoms ^f	10.3 $\pm$ 9.3	7.1 $\pm$ 7.6	8.6 $\pm$ 8.7	11.9 $\pm$ 10.9
Body mass index ^g	26.0 $\pm$ 5.3	26.1 $\pm$ 4.0	26.3 $\pm$ 5.1	25.8 $\pm$ 5.7
Nursing home resident (month prior to ICU admission)	22 (8.3)	0 (0)	8 (7.0)	14 (11.7)
Type of ICU				
MICU	101 (38.0)	6 (18.8)	43 (37.7)	52 (43.3)
SICU/CTICU	53 (19.9)	9 (28.1)	29 (25.4)	15 (12.5)
CCU	100 (37.6)	14 (43.8)	34 (29.8)	52 (43.3)
Other	12 (4.5)	3 (9.4)	8 (7.0)	1 (0.8)
ICU length of stay, d ^h	2.9 $\pm$ 4.1	3.5 $\pm$ 4.4	3.0 $\pm$ 5.5	2.6 $\pm$ 2.1
Use of mechanical ventilation ⁱ	46 (17.3)	3 (9.4)	12 (10.5)	16 (13.5)
Shock ⁱ	12 (4.5)	0 (0)	2 (1.8)	10 (8.3)

CCU = coronary care unit; MICU = general/medical ICU; SICU/CTICU = surgical/cardi thoracic ICU.

^aThe 266 ICU admissions were contributed by 215 participants.

^bThe five Fried frailty criteria are weight loss, exhaustion, muscle weakness, slow gait speed, and low physical activity. Frailty, prefrailty, and nonfrailty were defined, respectively, as 3 to 5, 1 or 2, and 0 positive criteria.

^cHypertension, myocardial infarction, heart failure, stroke, diabetes mellitus, arthritis, hip fracture, chronic lung disease, and cancer (other than minor skin cancers).

^dFrom the month prior to ICU admission (range, 0 to 13): four activities of daily living (bathing, dressing, walking, and transferring), five instrumental activities (shopping, housework, meal preparation, taking medications, and managing finances), and four mobility activities (walk one-quarter mile, climb a flight of stairs, lift or carry 10 pounds, and drive in the past month).

^eFolstein Mini-Mental State Exam (MMSE)²⁸ score < 24. MMSE scores range from 0 to 30, with higher scores representing better cognitive function.

^fCenter for Epidemiological Studies Depression Scale (CES-D)²⁹: A modified nine-item version of the 11-item CES-D scale was used, which excluded the two questions used in the Fried frailty exhaustion criterion. Scores of this shorter version were transformed to correspond to the standard 20-item scale.

^gSelf-reported height and weight (kg/m²).

^hWhen data were available from Medicare claims, ICU length of stay was based on the number of days billed in a critical care unit. For participants in managed Medicare, ICU length of stay was abstracted from the medical record.

ⁱAscertained using ICD-9 codes and chart review, as described in Methods.

worsened, including age, pre-ICU disability count, and markers of ICU severity of illness.

The disability counts by Fried frailty status are presented in Figure 2. Although the disability count worsened considerably for all three groups in the setting of an ICU admission, recovery after the critical illness differed by frailty status, with the nonfrail group returning close to their pre-ICU level of function, in contrast to the frail and prefrail groups. The results for the three disability subscales (ADLs, IADLs, and mobility) were comparable (e-Figs 1-3). In the multivariable analysis, frailty was associated with 41% greater disability over the 6 months following a critical illness (RR, 1.41; 95% CI, 1.12-1.78) relative to nonfrailty. Prefrailty conferred a 28% greater risk of post-ICU disability (RR, 1.28; 95% CI, 1.01-1.63) relative to nonfrailty. In the sensitivity analyses, the associations between Fried frailty status and post-ICU disability remained robust to the competing risk of death (e-Table 1).

Descriptive statistics for the secondary outcomes are provided in Table 2. The rate of incident nursing home admission increased as frailty status worsened: not frail, 23.5%; prefrail, 37.7%; and frail, 58.8%. In the multivariable analysis, frailty was significantly associated with incident nursing home admission (odds ratio, 3.52; 95% CI, 1.23-10.08), whereas prefrailty was not (odds

ratio, 2.01; 95% CI, 0.77-5.24). In the sensitivity analyses, the association between frailty and incident nursing home admission remained statistically significant, except for the least likely imputation where none of the decedents develop the outcome, while the absence of association between prefrailty and incident nursing home admission was maintained (e-Table 2).

Mortality from ICU admission through 6 months of follow-up was twice as high among participants with frailty (54.5%) as compared with those who were prefrail (25.0%) or nonfrail (26.3%). Survival by Fried frailty status is presented in Figure 3. The log-rank test demonstrated a statistically significant survival difference across the frailty groups ($P < .001$). In the final multivariable model, which evaluated Fried frailty count (0-5) due to better functional form, each one-point increase was associated with double the hazard of death over the 6 months after an ICU admission (hazard ratio, 2.00; 95% CI, 1.33-3.00).

Discussion

In this longitudinal study of older persons, we found that frailty status prior to ICU admission was strongly associated with the course of post-ICU disability, incident nursing home admission, and death from ICU admission through 6 months of follow-up, after adjustment for a comprehensive set of covariates. Among ICU survivors, frailty and prefrailty were associated with 41% and 28% greater disability over the 6 months following a critical illness, respectively, relative to nonfrailty. Among community-living participants who survived to hospital discharge, those who were frail were more than three times as likely to be discharged to a nursing home, relative to those who were nonfrail. Finally, more than one-half of the frail participants died within 6 months of their ICU admission, and each one-point increase in the Fried frailty count (0-5) was associated with double the risk of death over the follow-up period.

In studies of community-living and hospitalized older adults, premorbid frailty, most commonly measured with the Fried frailty index,¹² has been widely studied as a contributing factor to poor outcomes.^{9,11} However, because of the inherent difficulty of evaluating frailty retrospectively in the setting of critical illness, less is known about the role of pre-ICU frailty in post-ICU outcomes. Although the Clinical Frailty Scale has been administered successfully during ICU admission,^{13,14} this instrument includes indicators of disability, thereby

Figure 2 – Pre- and post-ICU disability count by frailty status (N = 266) over 6 months of post-ICU follow-up. Values (ranging from 0 to 13) are unadjusted and error bars represent standard deviations. As a reference point, the pre-ICU disability counts (from the month prior to ICU admission) are included at month 0. The 266 ICU admissions were contributed by 215 participants who survived to their first post-ICU monthly interview. The number of survivors alive at each month of follow-up by frailty status is presented below the figure. There was no attrition for reasons other than death.

TABLE 2] Characteristics of ICU Admissions Contributed by Participants Eligible for the Secondary Outcomes according to Pre-ICU Fried Frailty Status^a

Characteristic	Incident NH Admission (N = 267) ^b			All-Cause Mortality (N = 391) ^c		
	Not Frail (n = 34)	Prefrail (n = 114)	Frail (n = 119)	Not Frail (n = 38)	Prefrail (n = 140)	Frail (n = 213)
Age, mean $\pm$ SD, y	80.0 $\pm$ 3.9	82.6 $\pm$ 5.1	85.3 $\pm$ 5.5	80.3 $\pm$ 3.8	82.9 $\pm$ 5.0	86.1 $\pm$ 5.5
Female sex, No. (%)	18 (52.9)	65 (57.0)	75 (63.0)	19 (50.0)	79 (56.4)	133 (62.4)
Non-Hispanic white, No. (%)	30 (88.2)	99 (86.8)	106 (89.1)	34 (89.5)	125 (89.3)	184 (86.4)
Education, mean $\pm$ SD, y	12.7 $\pm$ 2.4	12.3 $\pm$ 3.0	11.6 $\pm$ 2.9	12.9 $\pm$ 2.5	12.3 $\pm$ 3.0	11.5 $\pm$ 3.1
Cognitive function by MMSE score, ^d mean $\pm$ SD	27.4 $\pm$ 2.2	26.9 $\pm$ 2.5	24.7 $\pm$ 3.9	27.5 $\pm$ 2.2	26.8 $\pm$ 2.8	23.5 $\pm$ 5.4
Chronic conditions, ^e mean $\pm$ SD	2.1 $\pm$ 1.0	2.2 $\pm$ 1.3	2.8 $\pm$ 1.3	2.1 $\pm$ 1.0	2.3 $\pm$ 1.3	2.7 $\pm$ 1.4
Pre-ICU disability, ^f mean $\pm$ SD	1.9 $\pm$ 2.3	2.9 $\pm$ 2.6	6.6 $\pm$ 3.4	2.7 $\pm$ 3.3	3.7 $\pm$ 3.4	8.1 $\pm$ 3.8
Depressive symptoms, ^g mean $\pm$ SD	7.3 $\pm$ 7.7	8.5 $\pm$ 8.6	12.1 $\pm$ 11.0	7.4 $\pm$ 7.8	8.4 $\pm$ 8.5	12.6 $\pm$ 10.9
Body mass index, ^h mean $\pm$ SD	25.8 $\pm$ 4.1	26.1 $\pm$ 4.9	26.1 $\pm$ 5.8	26.1 $\pm$ 4.0	26.0 $\pm$ 5.0	25.7 $\pm$ 6.3
Nursing home resident in the month prior to ICU admission, No. (%)	N/A	N/A	N/A	2 (5.3)	13 (9.3)	56 (26.3)
Type of ICU, No. (%)						
General/MICU	7 (20.6)	40 (35.1)	51 (42.9)	9 (23.7)	54 (38.6)	103 (48.4)
SICU/CTICU	9 (26.5)	29 (25.4)	16 (13.5)	9 (23.7)	36 (25.7)	32 (15.0)
CCU	14 (41.2)	35 (30.7)	49 (41.2)	16 (42.1)	39 (27.9)	71 (33.3)
Other	4 (11.8)	10 (8.8)	3 (2.5)	4 (10.5)	11 (7.9)	7 (3.3)
ICU length of stay, ⁱ mean $\pm$ SD	4.9 $\pm$ 8.2	3.2 $\pm$ 5.6	2.7 $\pm$ 2.1	5.0 $\pm$ 7.9	4.3 $\pm$ 7.2	3.2 $\pm$ 3.0
Use of mechanical ventilation, ^j No. (%)	5 (14.7)	14 (12.3)	15 (12.7)	8 (21.1)	27 (19.3)	58 (27.5)
Shock, ^j No. (%)	0 (0)	3 (2.6)	10 (8.4)	2 (5.3)	8 (5.7)	32 (15.0)

N/A = not applicable; NH = nursing home. See Table 1 legend for expansion of other abbreviations.

^aThe five Fried frailty criteria are weight loss, exhaustion, muscle weakness, slow gait speed, and low physical activity. Frailty, prefrailty, and nonfrailty were defined, respectively, as 3 to 5, 1 or 2, and 0 positive criteria.

^bThe 267 ICU admissions were contributed by 216 participants. Only ICU admissions where the participant was community-dwelling prior to hospital admission and survived to hospital discharge were eligible for the outcome of incident nursing home admission.

^cThe 391 ICU admissions were contributed by 303 participants. Because the ICU admission date was not available in Medicare claims, the hospital admission date was used as a proxy.

^dMeasured with the Folstein Mini-Mental State Exam (MMSE)²⁸: Scores range from 0 to 30, with higher scores representing better cognitive function.

^eOf a possible nine: hypertension, myocardial infarction, heart failure, stroke, diabetes mellitus, arthritis, hip fracture, chronic lung disease, and cancer (other than minor skin cancers).

^fFrom the month prior to ICU admission, assessed in each of 13 functional activities: four activities of daily living (bathing, dressing, walking, and transferring), five instrumental activities (shopping, housework, meal preparation, taking medications, and managing finances), and four mobility activities (walk one-quarter mile, climb a flight of stairs, lift or carry 10 pounds, and drive in the past month).

^gCenter for Epidemiological Studies Depression Scale (CES-D)²⁹: A modified nine-item version of the 11-item CES-D scale was used, which excluded the two questions used in the Fried frailty exhaustion criterion. Scores of this shorter version were transformed to correspond to the standard 20-item scale.

^hSelf-reported height and weight (kg/m²).

ⁱWhen data were available from Medicare claims, ICU length of stay was based on the number of days billed in a critical care unit. For participants in managed Medicare, ICU length of stay was abstracted from the medical record.

^jAscertained using ICD-9 codes and chart review, as described in Methods.

Figure 3 – Kaplan-Meier graph demonstrating survival by frailty group from admission through 6 months of posthospital follow-up ($N = 391$). Group sizes were: not frail, $n = 38$ (9.7%); prefrail, $n = 140$ (35.8%); and frail, $n = 213$ (54.5%). Because the ICU admission date was not available in Medicare claims, the hospital admission date was used as a proxy. Follow-up extended to 210 days because each ICU admission was nested within a hospitalization, which sometimes extended beyond 30 days. The vertical tick marks represent censored observations.

conflating premorbid frailty and disability. Although the two conditions can overlap, frailty is distinct from disability,^{10,30} and maintaining this distinction in a frailty assessment tool is particularly important when evaluating disability as an outcome. Our study addresses the limitations of prior work by evaluating, for the first time, the association of Fried frailty, measured prior to the critical illness, with post-ICU outcomes, including disability. While we recognize that administration of the Fried frailty index may often not be feasible in a critically ill patient,³¹ recent work has demonstrated that surrogates can usually answer questions about Fried frailty markers, making proxy-based assessments feasible in the ICU.³² Moreover, the Fried frailty index can be administered in primary care settings to help inform prospective goals of care discussions with older patients and their families. Future research is needed to develop and validate a frailty measure that can be routinely used in the setting of a critical illness while maintaining the distinction between disability and frailty in its operationalization.

Our results may help to inform the design of future studies evaluating restorative interventions, such as early mobilization programs, that are designed to improve post-ICU functional outcomes among ICU survivors. Trials attempting to improve long-term outcomes after a critical illness have yielded mixed results,³³⁻³⁶ prompting discussion about the need to identify subgroups of the

ICU population who are at risk for poor outcomes and yet still capable of benefiting from the intervention being tested.³⁷⁻³⁹ The current study demonstrates that functional outcomes after a critical illness differ by pre-ICU frailty status, and builds on our prior work, which demonstrated the importance of other pre-ICU factors, such as sensory impairments, in functional outcomes after critical illness.^{16,22} In future clinical trials of restorative interventions, one might consider stratifying patients by pre-ICU vulnerability factors such as frailty status, rather than by ICU factors, as has been done previously.³⁹ This strategy may help to identify which patients are most likely to benefit from restorative interventions. Researchers could also investigate whether the level and intensity of the restorative program should be tailored based on pre-ICU vulnerability factors.

A major strength of our study is its prospective, longitudinal design, which allowed us to objectively assess frailty status prior to the ICU admission and evaluate its association with post-ICU outcomes. Additional strengths include the following: (1) the use of the Fried frailty index, the most widely used frailty assessment tool in the literature¹²; (2) the evaluation and consistency of results across multiple domains of post-ICU disability (ADLs, IADLs, and mobility disability); (3) the inclusion of three distinct patient-centered outcomes (post-ICU disability, new nursing home admission, and mortality); (4) the advanced age of the study population; (5) the minimal attrition for reasons other than death; (6) the inclusion of patients with managed Medicare; and (7) an analytic strategy that tested for bias due to the competing risk of death.

Our study had several limitations. First, because frailty was assessed every 18 months, it is possible that frailty status may have changed between the time it was assessed and ICU admission. However, changes in frailty occur most commonly in the setting of an acute hospitalization,⁴⁰ resulting in worsening frailty, which would have biased our results toward the null. Second, while our analyses adjusted for three indicators of ICU severity of illness (mechanical ventilation, shock, and ICU length of stay), data were not available for standard scales such as the APACHE (Acute Physiology and Chronic Health Evaluation) II. Third, we did not have information on code status or limitations on life-sustaining treatment, which may have varied by frailty status. Participants who had restrictions on life-sustaining treatment during their ICU admission may

have been more likely to die in the hospital. Finally, because participants were drawn from one geographic region, our results may not be generalizable to people in other settings. However, the demographics of our cohort reflect those of older people in greater New Haven County, Connecticut, which are similar to the US population with the exception of race or ethnicity.⁴¹

In summary, frailty status prior to ICU admission was strongly associated with the subsequent course of post-ICU disability, incident nursing home admission, and death from ICU admission through 6 months of follow-up. Knowledge of pre-ICU frailty status may provide important prognostic information about outcomes after a critical illness.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

References

- Administration on Aging, Administration for Community Living, U.S. Department of Health and Human Services. A profile of older Americans: 2015. <https://www.acl.gov/sites/default/files/Aging%20and%20Disability%20in%20America/2015-Profile.pdf>. Accessed February 8, 2017.
- Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr; Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284(21):2762-2770.
- Brummel NE, Balas MC, Morandi A, Ferrante LE, Gill TM, Ely EW. Understanding and reducing disability in older adults following critical illness. *Crit Care Med*. 2015;43(6):1265-1275.
- Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
- Fried LP, Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. *J Am Geriatr Soc*. 1997;45(1):92-100.
- Fried TR, Tinetti ME, Iannone L, O'Leary JR, Towle V, Van Ness PH. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. *Arch Intern Med*. 2011;171(20):1854-1856.
- Hermans G, Van Mechelen H, Clerckx B, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2014;190(4):410-420.
- Herridge MS, Chu LM, Matte A, et al. The RECOVER program: disability: risk groups and 1-year outcome after 7 or more days of mechanical ventilation. *Am J Respir Crit Care Med*. 2016;194(7):831-844.
- Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A Biol Sci Med Sci*. 2001;56(3):M146-M156.
- Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol Ser A Biol Sci Med Sci*. 2004;59(3):255-263.
- Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762.
- Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev*. 2016;2653-2661.
- Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ*. 2014;186(2):E95-E102.
- Brummel NE, Bell SP, Girard TD, et al. Frailty and subsequent disability and mortality among patients with critical illness. *Am J Respir Crit Care Med*. 2017;196(1):64-72.
- Gill TM, Desai MM, Gahbauer EA, Holford TR, Williams CS. Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. *Ann Intern Med*. 2001;135(5):313-321.
- Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors associated with functional recovery among older intensive care unit survivors. *Am J Respir Crit Care Med*. 2016;194(3):299-307.
- Gill TM, Hardy SE, Williams CS. Underestimation of disability in community-living older persons. *J Am Geriatr Soc*. 2002;50(9):1492-1497.
- Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med*. 2006;166(4):418-423.
- Gill TM, Gahbauer EA, Murphy TE, Han L, Allore HG. Risk factors and precipitants of long-term disability in community mobility a cohort study of older persons. *Ann Intern Med*. 2012;156(2):131-140.
- Gill TM, Guo Z, Allore HG. Subtypes of disability in older persons over the course of nearly 8 years. *J Am Geriatr Soc*. 2008;56(3):436-443.
- Kahn JM, Benson NM, Appleby D, Carson SS, Iwashyna TJ. Long-term acute care hospital utilization after critical illness. *JAMA*. 2010;303(22):2253-2259.
- Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. *JAMA Intern Med*. 2015;175(4):523-529.
- Sjoding MW, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Longitudinal changes in ICU admissions among elderly patients in the United States. *Crit Care Med*. 2016;44(7):1353-1360.
- Ferrante LE, Murphy TE, Gahbauer EA, Leo-Summers LS, Pisani MA, Gill TM. Pre-Intensive care unit cognitive status, subsequent disability, and new nursing home admission among critically ill older adults. *Ann Am Thor Soc*. 2018;15:622-629.
- Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med*. 2011;183(8):1037-1042.

26. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*. 1993;80(3):557-572.
27. Cox DR, Oakes D. *Monographs on Statistics and Applied Probability, Vol. 21: Analysis of Survival Data*. Boca Raton, FL: CRC Press; 1984.
28. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: practical method for grading cognitive state of patients for clinician. *J Psychiatr Res*. 1975;12(3): 189-198.
29. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health*. 1993;5(2):179-193.
30. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397.
31. Le Maguet P, Roquilly A, Lasocki S, et al. Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study. *Intensive Care Med*. 2014;40(5): 674-682.
32. Hope AA, Hsieh SJ, Petti A, Hurtado-Sbordoni M, Verghese J, Gong MN. Assessing the usefulness and validity of frailty markers in critically ill adults. *Ann Am Thorac Soc*. 2017;14(6):952-959.
33. Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2016;193(10):1101-1110.
34. Walsh TS, Salisbury LG, Merriweather JL, et al; RECOVER Investigators. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *JAMA Intern Med*. 2015;175(6):901-910.
35. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care*. 2013;17(4):R156.
36. Cuthbertson BH, Rattray J, Campbell MK, et al; PRaCTICaL Study Group. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ*. 2009;339:b3723.
37. Hodgson CL, Iwashyna TJ, Schweickert WD. All that work and no gain: what should we do to restore physical function in our survivors? *Am J Respir Crit Care Med*. 2016;193(10): 1071-1072.
38. Hodgson CL, Fan E. Better measures, better trials, better outcomes in survivors of critical illness. *Crit Care Med*. 2016;44(6):1254-1255.
39. Goddard SL, Adhikari NK. The challenging task of improving the recovery of ICU survivors. *JAMA*. 2016;315(24): 2671-2672.
40. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. *J Gerontol Ser A Biol Sci Med Sci*. 2011;66(11):1238-1243.
41. Gill TM, Allore HG, Holford TR, Guo ZC. Hospitalization, restricted activity, and the development of disability among older persons. *JAMA*. 2004;292(17):2115-2124.