Original Investigation

Functional Trajectories Among Older Persons Before and After Critical Illness

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IMPORTANCE Little is known about functional trajectories of older persons in the year before and after admission to the intensive care unit (ICU) or how pre-ICU functional trajectories affect post-ICU functional trajectories and death.

OBJECTIVES To characterize functional trajectories in the year before and after ICU admission and to evaluate the associations among pre-ICU functional trajectories and post-ICU functional trajectories, short-term mortality, and long-term mortality.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 754 community-dwelling persons 70 years or older, conducted between March 23, 1998, and December 31, 2012, in greater New Haven, Connecticut. The analytic sample included 291 participants who had at least 1 admission to an ICU through December 2011.

MAIN OUTCOMES AND MEASURES Functional trajectories in the year before and after an ICU admission based on 13 basic, instrumental, and mobility activities. Additional outcomes included short-term (30 day) and long-term (1 year) mortality.

RESULTS The mean (SD) age of participants was 83.7 (5.5) years. Three distinct pre-ICU functional trajectories identified were minimal disability (29.6%), mild to moderate disability (44.0%), and severe disability (26.5%). Seventy participants (24.1%) experienced early death, defined as death in the hospital (50 participants [17.2%]) or death after hospital discharge but within 30 days of admission (20 participants [6.9%]). Among the remaining 221 participants, 3 distinct post-ICU functional trajectories identified were minimal disability (20.8%), mild to moderate disability (28.1%), and severe disability (51.1%). More than half of the participants (53.4%) experienced functional decline or early death after critical illness. The pre-ICU functional trajectories of mild to moderate disability and severe disability were associated with more than double (adjusted hazard ratio [HR], 2.41; 95% CI, 1.29-4.50) and triple (adjusted HR, 3.84; 95% CI, 1.84-8.03) the risk of death within 1 year of ICU admission, respectively. Other factors associated with 1-year mortality included ICU length of stay (adjusted HR, 1.03; 95% CI, 1.00-1.05), mechanical ventilation (adjusted HR, 2.89; 95% CI, 1.91-4.37), and shock (adjusted HR, 2.68; 95% CI, 1.63-4.38).

CONCLUSIONS AND RELEVANCE Among older persons with critical illness, more than half died within 1 month or experienced significant functional decline over the following year, with particularly poor outcomes in those who had high levels of premorbid disability. These results may help to inform discussions about prognosis and goals of care before and during critical illness.

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As the population ages, the number of older persons in intensive care units (ICUs) is rising.[1,2] More than half of all ICU days are incurred by patients 65 years or older.[3] Advances in critical care medicine have allowed an increasing number of patients to survive what had previously been fatal illnesses. A growing body of research has demonstrated that ICU survivors experience significant long-term morbidity, resulting in enormous physical, emotional, cognitive, and financial burdens to patients, families, and society.[4-9] For the 1.4 million older adults who survive critical illnesses each year, understanding their subsequent functional course, and how their pre-ICU functional trajectory might influence this course, is invaluable.

To date, few studies have characterized functional trajectories before and after critical illness in older persons. Most investigations assessing functional outcomes have enrolled patients at ICU admission and evaluated pre-ICU function using retrospective assessments, often by proxy.[10-23] This imprecise assessment of premorbid function may overestimate the effects of critical illness on subsequent outcomes.[24,25] It has been suggested that the ideal design to evaluate post-ICU functional outcomes is a prospective longitudinal study in which only a subset of participants experience critical illness.[24]

To address the limitations of prior research, we used data from a unique longitudinal study of older persons who have been followed monthly for almost 15 years, providing us with the opportunity to rigorously evaluate the course of disability surrounding critical illness. Our objectives were 3-fold: first, to identify distinct functional trajectories in the year before and after critical illness; second, to evaluate the probability of transitioning between these trajectories in the setting of critical illness; and third, to identify factors independently associated with short-term and long-term mortality after critical illness, including ICU variables, clinical geriatric variables, and pre-ICU functional trajectories.

Methods

Study Population

The Yale Human Investigation Committee approved the study. All participants provided oral informed consent. Participants were drawn from the Precipitating Events Project, an ongoing longitudinal study described in detail elsewhere,[26,27] of 754 community-dwelling persons 70 years or older who were initially nondisabled in 4 basic activities of daily living (bathing, dressing, walking across a room, and transferring from a chair). The assembly of the cohort, which took place between March 23, 1998, and October 26, 1999, has been described in detail elsewhere.[26,28,29] The participation rate was greater than 75%.

Data Collection

Comprehensive home-based assessments were completed at baseline and at 18-month intervals for 162 months (except for at 126 months). Telephone interviews were completed monthly through December 31, 2012. For participants who had significant cognitive impairment or who were unavailable, a proxy informant was interviewed.[29] Deaths were ascertained by review of obituaries or from an informant during a telephone interview, with a completion rate of 100%. A total of 566 participants (75.1%) had died after a median follow-up of 90 months, while 41 participants (5.4%) dropped out of the study after a median follow-up of 27 months. Data were otherwise available for 99.1% of 78 391 monthly interviews. During the in-home assessments, data were obtained on demographics; 9 self-reported, physician-diagnosed chronic conditions; cognitive status; depressive symptoms; and physical frailty.[28] *Cognitive impairment* was defined as a score of less than 24 on the Mini-Mental State Examination,[30] while *depression* was defined as a score of 20 or higher on the Center for Epidemiological Studies Depression Scale.[31]

Assessment of Disability

During the monthly interviews, participants were asked, "At the present time, do you need help from another person to [complete the task]?" They were asked this question for each of 4 basic activities (bathing, dressing, walking across a room, and transferring from a chair), 5 instrumental activities (shopping, housework, meal preparation, taking medications, and managing finances), and 3 mobility activities (walk a quarter mile, climb a flight of stairs, and lift or carry 10 lb). Disability was operationalized as the need for personal assistance or an inability to perform the task. Participants were also asked about a fourth mobility activity, "Have you driven a car during the past month?" Participants who responded no were classified as being disabled in driving.[32] The primary outcome was the number of disabilities in all 13 basic, instrumental, and mobility activities. To address the small amount of missing disability data, we used multiple imputation, with 100 random draws per missing observation.[33]

Ascertainment of ICU Admissions

For most of the sample (75.3%), we used linked Medicare claims data to ascertain ICU admissions. We defined *ICU admission* as the presence of any critical care revenue code, including general, specialty, and coronary care units and excluding psychiatric or intermediate critical care.[34] For participants enrolled in Medicare Managed Care, information on hospitalizations was obtained during the monthly interviews. Participants were asked whether they had stayed overnight in a hospital since the previous month's interview. The accuracy of these reports based on an independent review of hospital records was high, with a sensitivity of 93.3% (95% CI, 90.5%-96.1%) and a specificity of 99.3% (95% CI, 99.0%-99.6%).[35] All self-reported hospitalizations were then evaluated for ICU admission through medical record review, which was completed by a critical care physician (L.E.F.) or a research nurse under the supervision of the critical care physician. Participants were identified as being critically ill based on documentation by the ICU physicians responsible for the care of the patient.

Acquisition of ICU Data

For all ICU admissions, additional data were obtained, including ICU length of stay, ICU service, presence of shock, use of mechanical ventilation, and primary discharge diagnosis. When claims data were available, ICU length of stay was based on the number of days billed for critical care. The remaining information was obtained from *International Classification of Diseases, Ninth Revision* codes.[36-38]

For participants enrolled in Medicare Managed Care, ICU variables were abstracted from the medical record. Mechanical ventilation was coded if the patient was intubated for respiratory failure or airway protection. Intubations for surgical procedures were excluded except when the patient was unable to be weaned from the ventilator within 12 hours. Shock was classified as present based on the attending ICU physician's assessment.

Assembly of the Analytic Sample

The analytic sample included participants who had at least 1 ICU admission from their enrollment date through 2011, allowing 1 year of follow-up. For each participant, only the first ICU admission was included.

Statistical Analysis

Demographic and clinical characteristics of 291 participants who had at least 1 admission to an ICU through December 2011 were recorded. Functional trajectories were based on the number of disabilities (range, 0-13). To identify distinct functional trajectories in the year immediately before and after ICU admission, we used a form of latent class analysis called trajectory modeling.[39] The PROC TRAJ macro[40,41] (SAS, version 9.3; SAS Institute Inc[42]) was run with a zero-inflated Poisson distribution and no adjustment for covariates. This method first estimates each participant's probability of membership in multiple trajectories and then assigns the participant to the trajectory with the highest probability of membership. Based on statistical and clinical criteria described elsewhere,[43,44] 3 functional trajectories were found to be optimal in the year before and after ICU admission. The unadjusted least squares means of disability within each functional trajectory were plotted for each month.

Next, the post-ICU functional trajectory modeling was repeated with adjustment for the following covariates: age, sex, years of education, race, number of chronic conditions, primary discharge diagnosis of cardiac disease, ICU length of stay, mechanical ventilation, shock, cognitive impairment, depression, and physical frailty. Using 1000 bootstrapped samples,[45] we calculated the probability of membership in each post-ICU functional trajectory conditional on membership in a given pre-ICU functional trajectory. To account for all participants, death within 30 days was included as a post-ICU outcome. As a sensitivity analysis, ICU service was added to the adjusted model.

Our secondary outcomes included short-term (30 day) and long-term (1 year) mortality. The unadjusted estimates were calculated as the proportions of participants dying within those intervals. Because the ICU admission date was not available in Medicare claims, the hospital admission date was used as a proxy. We then modeled the associations among pre-ICU functional trajectories and post-ICU functional trajectories, short-term mortality, and long-term mortality using multivariable Cox proportional hazards regression models, with minimal pre-ICU disability as the reference group. The multivariable mortality models included the same covariates as the adjusted post-ICU functional trajectory model. Time to death was measured from admission, and survivors were censored at 30 days and 12 months, respectively, for the short-term mortality and long-term mortality models.

All analyses were performed using statistical software (SAS, version 9.3; SAS Institute Inc). Statistical significance was defined at $P < .05$ (2-tailed).

Results

Table 1 lists the characteristics of 291 participants admitted to an ICU. The mean age was 83.7 years. More than half (58.1%) were female, and most (88.7%) were of non-Hispanic white race. Only 45 participants (15.5%) were admitted from a nursing home. At the start of the pre-ICU functional trajectory, the mean number of disabilities was 3.8. As shown in **Figure 1**A, 3 distinct functional trajectories were identified in the year before ICU admission, including minimal disability, mild to moderate disability, and severe disability. The severity of disability increased before ICU admission for the latter 2 groups but remained flat for the minimal disability group. Most of the characteristics in Table 1 worsened as the pre-ICU functional trajectory deteriorated.

Of 291 participants, 120 (41.2%) were admitted to a medical or general ICU, 48 (16.5%) to a surgical or cardiothoracic surgical ICU, 104 (35.7%) to a nonsurgical cardiac unit, and 19 (6.5%) to another ICU, most often a neurosurgical ICU or burn unit. Overall, 87 participants (29.9%) required mechanical ventilation, and shock was present in 30 participants (10.3%). The median number of ICU days was 2.0 (interquartile range, 1.0-4.0). The median number of hospital days was 7.0 (interquartile range, 4.0-12.0). Seventy participants (24.1%) experienced early death, defined as death in the hospital (50 participants [17.2%]) or death after hospital discharge but within 30 days of admission (20 participants [6.9%]). For the latter participants, the median time to death after hospital discharge was 9.5 (interquartile range, 5.0-14.0) days. Of 241 hospital survivors, 67 (27.8%) were discharged to home without services, 33 (13.7%) to home with services, 124 (51.5%) to a skilled nursing facility, 11 (4.6%) to inpatient rehabilitation, and 6 (2.5%) to hospice.

As shown in Figure 1B, 3 distinct post-ICU functional trajectories were identified, including minimal disability, mild to moderate disability, and severe disability. **Table 2** lists the adjusted probabilities of the post-ICU functional trajectories conditional on the pre-ICU functional trajectories. One-quarter of those with minimal pre-ICU disability became severely disabled or experienced early death after critical illness. Of those with mild to moderate pre-ICU disability, 39.5% transitioned to severe disability, while more than one-quarter experienced early death. Of those with severe pre-ICU disability, one-third experienced early death, and the rest remained severely disabled. Overall, 53.4% of the sample experienced functional decline or early death after critical illness. Type of ICU service did not affect these results.

Results of the multivariable short-term and long-term mortality models are shown in **Figure 2**. Thirty-day mortality was 21.0% (95% CI, 16.3%-25.6%) and increased with worsening severity of the pre-ICU functional trajectory from 8.1% (95% CI, 2.4%-13.9%) in the minimally disabled group, to 22.7% (95% CI,

Table 1. Characteristics of Participants With an ICU Admission

Characteristic	All Participants (n = 291)	Pre-ICU Functional Trajectory: Minimal Disability (n = 86)	Mild to Moderate Disability (n = 128)	Severe Disability (n = 77)
At the Time of ICU Admission				
Age, mean (SD), y	83.7 (5.5)	80.6 (4.7)	83.9 (5.3)	86.9 (4.7)
Female sex, No. (%)	**169** (58.1)	48 (55.8)	69 (53.9)	52 (67.5)
Non-Hispanic white race, No. (%)	**258** (88.7)	79 (91.9)	116 (90.6)	63 (81.8)
Did not complete high school, No. (%)	**101** (34.7)	25 (29.1)	45 (35.2)	31 (40.3)
Nursing home resident, No. (%)	**45** (15.5)	0	11 (8.6)	34 (44.2)
Before ICU Admission[a]				
Lives alone, No. (%)	**107** (36.8)	43 (50.0)	39 (30.5)	25 (32.5)
No. of chronic conditions, mean (SD)[b]	2.4 (1.3)	1.9 (1.1)	2.5 (1.3)	2.8 (1.4)
Body mass index, mean (SD)[c]	25.9 (5.7)	26.3 (5.4)	25.6 (5.5)	25.9 (6.3)
Cognitive impairment, No. (%)[d]	**56** (19.2)	7 (8.1)	24 (18.8)	25 (32.5)
Depression, No. (%)[e]	**53** (18.2)	11 (12.8)	18 (14.1)	24 (31.2)
Slow gait speed, No. (%)[f]	**164** (56.4)	14 (16.3)	78 (60.9)	72 (93.5)
No. of Disabilities at the Start of the Pre-ICU Functional Trajectory, Mean (SD)				
All activities, range 0-13	3.8 (3.7)	0.6 (1.0)	3.1 (2.2)	8.4 (3.2)
Basic activities, range 0-4	0.5 (1.1)	0.0 (0.2)	0.1 (0.6)	1.5 (1.0)
Instrumental activities, range 0-5	1.8 (1.8)	0.3 (0.6)	1.6 (1.3)	1.5 (4.0)
Mobility activities, range 0-4	1.5 (1.4)	0.3 (0.7)	1.4 (1.1)	3.1 (1.1)

Abbreviation: ICU, intensive care unit.

[a] Ascertained during the last comprehensive assessment before ICU admission.

[b] Of a possible 9 (hypertension, myocardial infarction, congestive heart failure, stroke, nonskin cancers, diabetes mellitus, fractures, arthritis, and chronic lung disease).

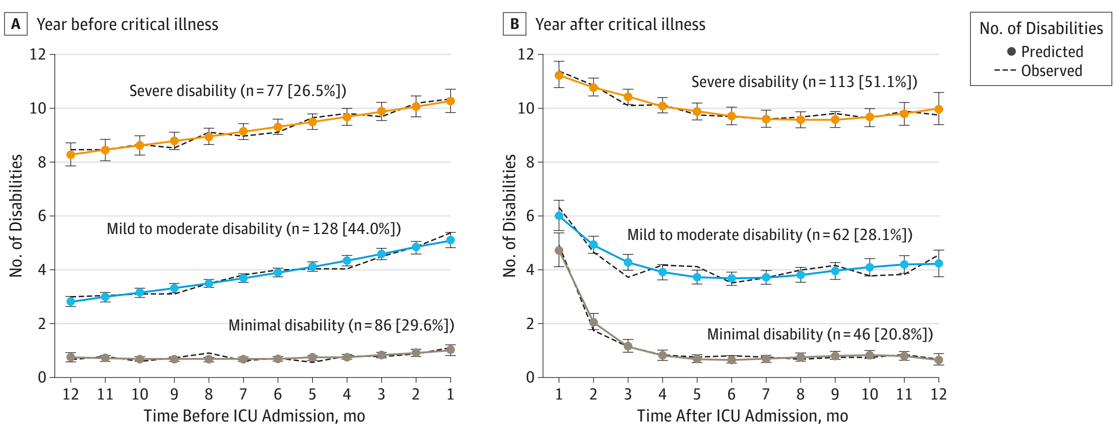
[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Defined as a score of less than 24 on the Mini-Mental State Examination.

[e] Defined as a score of 20 or higher on the Center for Epidemiological Studies Depression Scale.

[f] Defined as requiring more than 10 seconds to walk back and forth over a 3-meter course as quickly as possible.

Figure 1. Functional Trajectories Among Older Persons in the Year Before and After Critical Illness



The number of disabilities are expressed as least squares means (95% CIs); the possible number ranged from 0 to 13. Solid lines indicate predicted functional trajectories; dashed lines, observed functional trajectories. The average posterior probability of class membership for all 3 pre–intensive care unit (ICU) functional trajectories was 98%. The corresponding probabilities for the post-ICU functional trajectories were at least 98%. Among 221 participants who survived to 30 days after ICU admission, the number (percentage) of deaths in the subsequent year was 1 (2.2%), 2 (3.2%), and 52 (46.0%) for those with minimal, mild to moderate, and severe post-ICU disability, respectively, and the median time to death was 24, 258, and 106 days, respectively.

15.4%-29.9%) in the mild to moderately disabled group, and to 32.5% (95% CI, 22.0%-42.9%) in the severely disabled group. Significantly associated with 30-day mortality were mechanical ventilation (42.5% vs 11.8%; adjusted hazard ratio [HR], 3.28; 95% CI, 1.77-6.08), shock (66.7% vs 15.7%; adjusted HR, 3.91; 95% CI, 2.10-7.26), and cognitive impairment (30.4% vs 18.7%; adjusted HR, 2.05; 95% CI, 1.06-3.96) but not the pre-ICU functional trajectory (adjusted HRs, 1.88; 95% CI, 0.73-4.83 for mild to moderate disability and 2.13; 95% CI, 0.71-6.42 for severe disability).

One-year mortality was 43.0% (95% CI, 37.3%-48.7%) and increased with worsening severity of the pre-ICU functional trajectory from 18.6% (95% CI, 10.4%-26.8%) in the minimally disabled group, to 44.5% (95% CI, 35.9%-53.1%) in the mild to moderately disabled group, and to 67.5% (95% CI, 57.1%-78.0%) in the severely disabled group. Relative to minimal pre-ICU disability, the mild to moderate and severe pre-ICU functional trajectories were associated with more than double (adjusted HR, 2.41; 95% CI, 1.29-4.50) and triple (adjusted HR, 3.84; 95% CI, 1.84-8.03) the risk of death within 1 year of ICU admission, respectively. Other factors associated with 1-year mortality included ICU length of stay (adjusted HR, 1.03; 95% CI, 1.00-1.05), mechanical ventilation (77.0% vs 28.4%; ad-

Table 2. Adjusted Probabilities of Transitioning Between the Pre-ICU and Post-ICU Functional Trajectories[a]

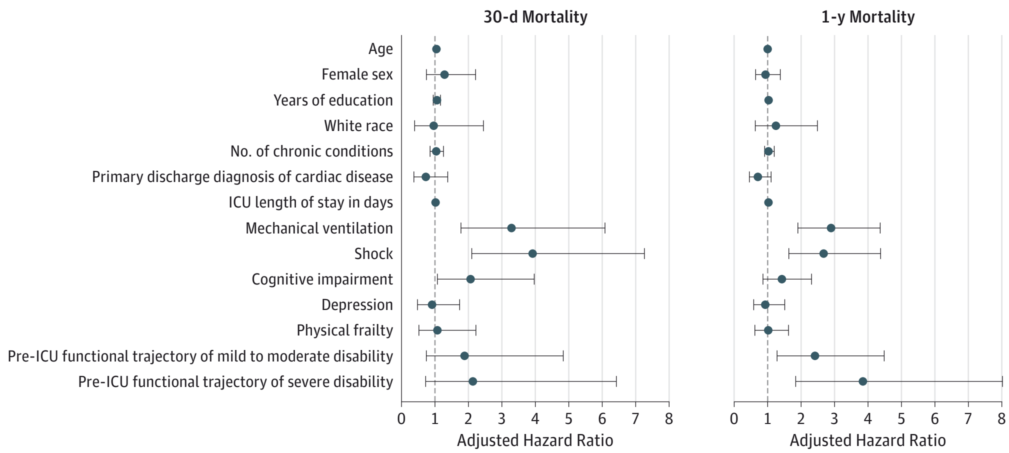
Pre-ICU Functional Trajectory	Post-ICU Functional Trajectory (95% CI)			
	Minimal Disability (n = 44)	Mild to Moderate Disability (n = 64)	Severe Disability (n = 113)	Early Death[b] (n = 70)
Minimal disability (n = 86)	0.49 (0.31-0.65)	0.27 (0.16-0.45)	0.13 (0.04-0.19)	0.12 (0.05-0.19)
Mild to moderate disability (n = 128)	0.02 (0.00-0.10)	0.32 (0.23-0.42)	0.40 (0.28-0.49)	0.26 (0.19-0.35)
Severe disability (n = 77)	0.00 (0.00-0.00)	0.00 (0.00-0.07)	0.66 (0.52-0.75)	0.34 (0.23-0.44)

Abbreviation: ICU, intensive care unit.

[a] Membership in the post-ICU functional trajectories was adjusted for the following covariates: age, sex, years of education, race, number of chronic conditions, primary discharge diagnosis of cardiac disease, ICU length of stay in days, mechanical ventilation, shock, cognitive impairment, depression, and physical frailty. Adjustment led to 2 participants moving from the post-ICU minimal disability group to the mild to moderate disability group.

[b] Early death was defined as death occurring within 30 days of the hospital admission date. This group includes those who died in the hospital (n = 50) and those who died after hospital discharge but within 30 days of hospital admission (n = 20).

Figure 2. Factors Associated With Short-term and Long-term Mortality After Critical Illness in Older Persons



The pre–intensive care unit (ICU) functional trajectory of minimal disability served as the reference group. The Cox proportional hazards regression model was adjusted for the first 12 factors listed in the figure. Time to death was measured from the day of hospital admission, and survivors were censored at 30 days and 1 year, respectively, for the short-term and long-term mortality models. The point estimates are accompanied by 95% CIs.

justed HR, 2.89; 95% CI, 1.91-4.37), and shock (90.0% vs 37.6%; adjusted HR, 2.68; 95% CI, 1.63-4.38).

Discussion

In this longitudinal study of older persons, we identified clinically distinct sets of functional trajectories in the year before and after ICU admission and determined the likelihood of transitioning between functional trajectories in the setting of critical illness. We found that more than half of the participants with critical illness died within 1 month or experienced significant functional decline over the following year, with particularly poor outcomes in those who had high levels of premorbid disability. We also found that the independent effect of the pre-ICU functional trajectories on 1-year mortality was comparable to that of mechanical ventilation and shock, 2 well-established indicators of the severity of critical illness. These results provide new information about the functional antecedents and consequences of critical illness in older persons and underscore the importance of the pre-ICU functional trajectory on the course of disability and mortality after critical illness.

These findings have significant clinical and public health importance because disability is associated with increased mortality, institutionalization, and greater use of formal and informal home services.[46] The poor outcomes among most participants suggest the need for improvements in ICU and post-ICU care for older adults, with a focus on maintaining function while treating acute illness. Additional research is needed to develop and test new rehabilitation strategies for older ICU survivors, with special attention to those who are more disabled after an episode of critical illness. These efforts could be facilitated through a disability assessment in the ICU and hospital wards. For example, aggressive rehabilitation may be warranted for older patients who had minimal or mild to moderate pre-ICU disability and were found to have severe disability on a post-ICU assessment. Alternatively, a palliative care approach might be considered for those who had severe premorbid disability given their high subsequent mortality and poor functional course.

Results of the present study may inform advance care planning discussions for older adults in the primary care and ICU settings. Our disability assessment, which includes basic, instrumental, and mobility activities, can be easily performed in the outpatient setting and is already a part of many geriatric visits. With this information, primary care physicians can categorize their older patients into one of the pre-event trajectories and counsel them about the likelihood of significant functional decline or death in the event of critical illness. In the ICU, our results may inform discussions with older patients and families about goals of care and prognosis because critical illness represents a time of great uncertainty regarding whether an older person may regain functional independence.

The major strength of our study is its prospective longitudinal design, with monthly assessments of functional status. To date, most studies[10-23] of critical illness have ascertained pre-ICU function retrospectively, often by proxy. Although 2 studies[4,6] evaluated premorbid function prospectively, these investigations were conducted in distinct populations of critically ill older persons. One study[6] used data from the Medicare Current Beneficiary Survey to demonstrate increased disability after mechanical ventilation. The other study[4] used data from the Health and Retirement Study to identify functional and cognitive deficits after severe sepsis, although most participants did not require ICU admission. However, functional status in the Medicare Current Beneficiary Survey and the Health and Retirement Study was assessed at 1-year and 2-year intervals, respectively, precluding the evaluation of short-term changes in function or the identification of trajectories. These studies were also limited by survivor bias because follow-up functional data cannot be obtained on participants who die between assessments. The availability of detailed information on functional status at monthly intervals before and after ICU admission allowed us to carefully characterize functional trajectories while more accurately evaluating the effect of pre-ICU functional trajectories on post-ICU function and death.

A second major strength is the advanced age of our study population, which is unique in studies of ICU outcomes and allowed us to provide new information on the course of disability and mortality in this expanding population of critically ill patients. Additional strengths include minimal attrition for reasons other than death and the complete ascertainment of ICU admissions through the use of claims data in addition to medical records, which enabled the inclusion of patients with Medicare Managed Care coverage, a population that has been excluded from some studies owing to the lack of claims data.[4,6,47] Finally, because admissions to the cardiac care unit were not omitted as they sometimes are in investigations of critical illness,[47] our results should be applicable across varying ICU settings. In a sensitivity analysis, adjustment for type of ICU service did not affect our results.

Despite these strengths, some limitations deserve comment. First, a small number of ICU admissions under Medicare Managed Care may have been missed because ascertainment of these hospitalizations was based on self-report. However, the accuracy of self-reported hospitalizations was high. Second, we had no information on code status and could not determine which patients had care withdrawn in the ICU. Those who had care withdrawn would likely have had shorter lengths of stay, with death occurring in the hospital. Third, the 95% CIs for the mortality models were wide owing to the modest sample size, which limited our ability to detect statistically significant differences for the associations between the pre-ICU functional trajectories and 30-day mortality. Fourth, information was unavailable on the receipt of restorative interventions that could have altered the course of recovery after critical illness. Fifth, because participants were drawn from a single urban area, our results may not be generalizable to older persons in other settings. However, the demographics of our cohort reflect those of older individuals in greater New Haven, Connecticut, which are similar to the demographics of the US population except for race.[48]

Conclusions

In summary, functional trajectories and death in the year following critical illness are strongly influenced by an older person's pre-ICU functional trajectory. For those who survive critical illness, the high likelihood of functional decline or death in the subsequent year underscores the risks and complexity of ICU survivorship. Further research is needed to elucidate the disabling and recovery process surrounding critical illness in older adults.

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Study concept and design: Ferrante, Gill.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ferrante, Murphy, Gahbauer.
Critical revision of the manuscript for important intellectual content: Ferrante, Pisani, Murphy, Gill.
Statistical analysis: Murphy, Gahbauer.
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