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Authors
Singer, Jonathan P
Lederer, David J
Baldwin, Matthew R

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Frailty in Pulmonary and Critical Care Medicine

Jonathan P. Singer[1], David J. Lederer[2,3], and Matthew R. Baldwin[4]

[1]Department of Medicine, University of California San Francisco, San Francisco, California; [2]Department of Medicine and [3]Department of Epidemiology, Columbia University Medical Center, New York, New York; and [4]Department of Medicine, Columbia University Medical Center, New York, New York

Abstract

Conceptualized first in the field of geriatrics, frailty is a syndrome characterized by a generalized vulnerability to stressors resulting from an accumulation of physiologic deficits across multiple interrelated systems. This accumulation of deficits results in poorer functional status and disability. Frailty is a "state of risk" for subsequent disproportionate declines in health status following new exposure to a physiologic stressor. Two predominant models have emerged to operationalize the measurement of frailty. The phenotype model defines frailty as a distinct clinical syndrome that includes conceptual domains such as strength, activity, wasting, and mobility. The cumulative deficit model defines frailty by enumerating the number of age-related things wrong with a person. The biological pathways driving frailty include chronic systemic inflammation, sarcopenia, and neuroendocrine dysregulation, among others. In adults with chronic lung disease, frailty is independently associated with more frequent exacerbations of lung disease, all-cause hospitalization, declines in functional status, and all-cause mortality. In addition, frail adults who become critically ill are more likely develop chronic critical illness or severe disability and have higher in-hospital and long-term mortality rates. The evaluation of frailty appears to provide important prognostic information above and beyond routinely collected measures in adults with chronic lung disease and the critically ill. The study of frailty in these populations, however, requires multipronged efforts aimed at refining clinical assessments, understanding the mechanisms, and developing therapeutic interventions.

Keywords: frailty; body composition; disability; health-related quality of life; mortality

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Correspondence and requests for reprints should be addressed to Jonathan P. Singer, M.D., M.S., 350 Parnassus Avenue, Suite 609, San Francisco, CA 94117. E-mail: jon.singer@ucsf.edu

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As early as the 1940s, geriatricians recognized subgroups of older adults whose functional limitations and age-related comorbid conditions appeared greater than could be expected by chronologic age alone (1). It was not until the early 21st century, however, that this phenomenon was defined by investigators, including Linda Fried and Kenneth Rockwood, as a distinct syndrome they termed "frailty" (2, 3).

Today, the most commonly referenced definition considers frailty to be an accumulation of physiologic deficits across multiple interrelated systems that results in both concurrent functional limitations and vulnerability to new stressors (2). Frailty represents a "state of risk" in which a relatively small stressor that might have otherwise been inconsequential exceeds the now-diminished physiologic reserves, resulting in a disproportionate (and potentially catastrophic) decline in health status.

In the field of geriatrics, frailty is associated with those outcomes most important to older adults—namely, the loss of the physical and cognitive functioning needed to maintain an independent lifestyle. Indeed, frailty not only is associated with prevalent physical and cognitive impairments but also identifies patients at increased risk for falls, hospitalization, institutionalization, poorer health-related quality of life, and death (2–10).

Conceptually, in pulmonary medicine, frail patients with lung disease may be at heightened risk for pulmonary exacerbations and, if exacerbations occur, may be more likely to experience greater loss of functioning and death (Figure 1A). In critical care medicine, frail patients who develop acute critical illness may be more likely to experience early mortality or, if they survive to discharge, may require prolonged or permanent institutionalization (Figure 1B). Recently, frailty has been identified as a risk factor for poor outcomes in adults with lung disease and critical illness—including those of younger age (6, 7, 11–17).

We review the pathobiology underpinning the frailty syndrome, a

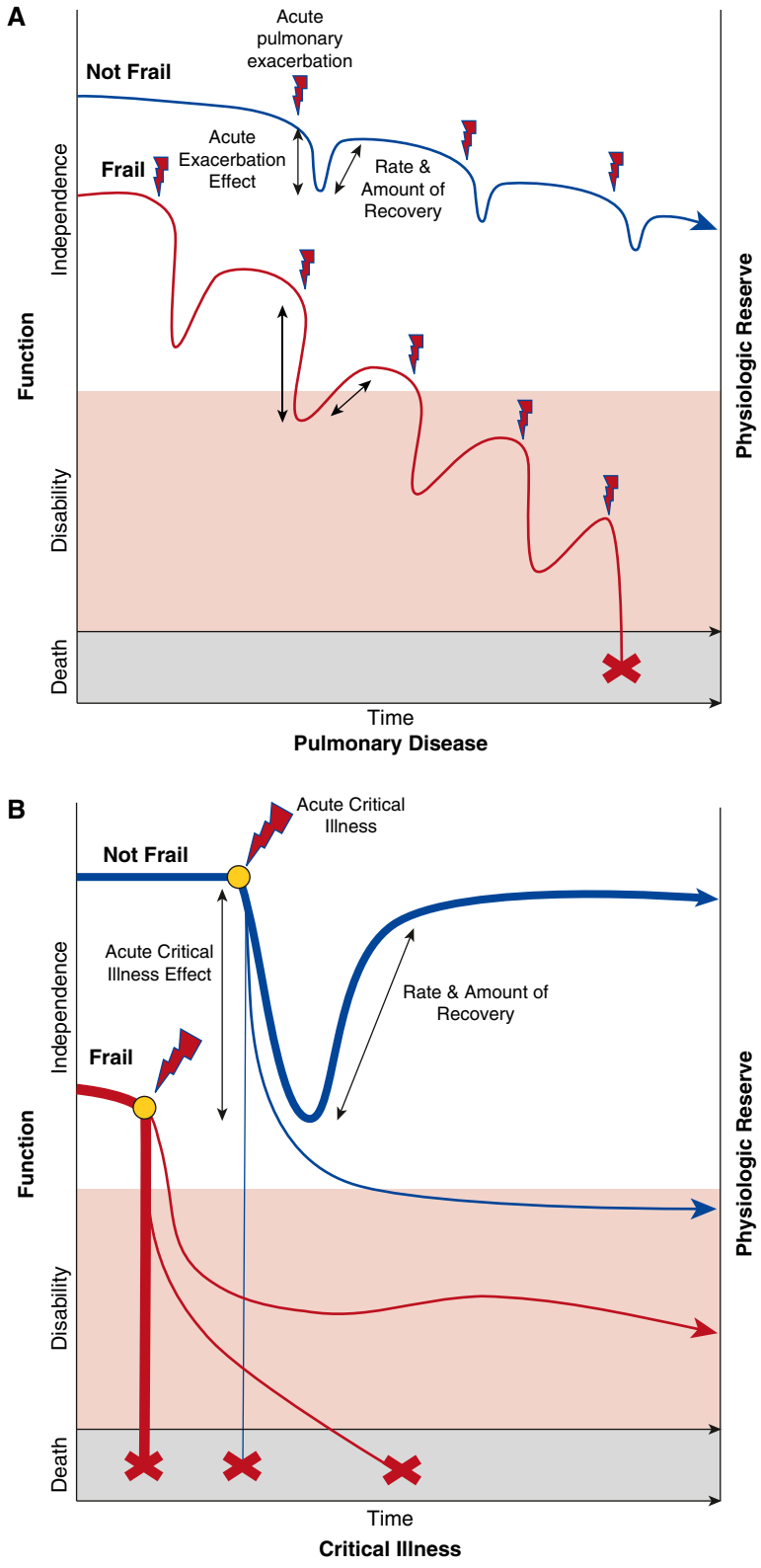

Figure 1. (*A*) Hypothetical trajectories of functional status for patients experiencing recurrent acute exacerbations of chronic lung disease who are frail (*red line*) and not frail (*blue line*). Frail patients are susceptible to more frequent exacerbations with less recovery in between, resulting in faster loss of functional status, earlier onset of disability, and a shorter lifespan. (*B*) Hypothetical trajectories for

number of instruments used to operationalize frailty measurement, and the associations between frailty and health outcomes in adults with lung disease and critical illness.

Pathobiology of Frailty

The putative mechanisms underlying frailty are multiple and reflect the complexity of the aging process. Although a detailed discussion is beyond the scope of this review, we highlight some of the potential mechanisms that, either individually or more likely in combination, cause frailty.

López-Otín and colleagues proposed nine molecular and cellular hallmarks of aging, which are themselves affected by genetic, epigenetic, and environmental factors (Figure 2) (18). In addition to these nine hallmarks of aging (i.e., immune senescence, mitochondrial dysfunction, telomere attrition), other putative causes of frailty include physical inactivity, malnutrition, and age-related diseases (e.g., dementia, osteoporosis). Either individually or in combination, these factors are believed to result in pathobiological perturbations such as chronic inflammation, immune senescence, endocrine dysregulation, and muscle dysfunction and sarcopenia (19). Once frailty develops, a new physiologic stressor (e.g., acute exacerbation of chronic obstructive pulmonary disease [COPD] or critical illness) can exceed the available physiologic reserves, resulting in disability, morbidity, and death.

Chronic systemic inflammation is considered to be one of the primary pathobiological changes driving frailty (20). First described in community-dwelling older adults, frail adults had increased serum levels of the proinflammatory cytokine IL-6 compared with nonfrail adults (21). Since then, others have identified associations between frailty and biomarkers of inflammation, including IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (22–27).

Because operational definitions of frailty involve deficits in functioning (i.e., slowness, weakness), abnormal muscle mass and function is also considered to be a fundamentally important cause of frailty (28). Sarcopenia is defined as abnormally low lean muscle mass combined with low

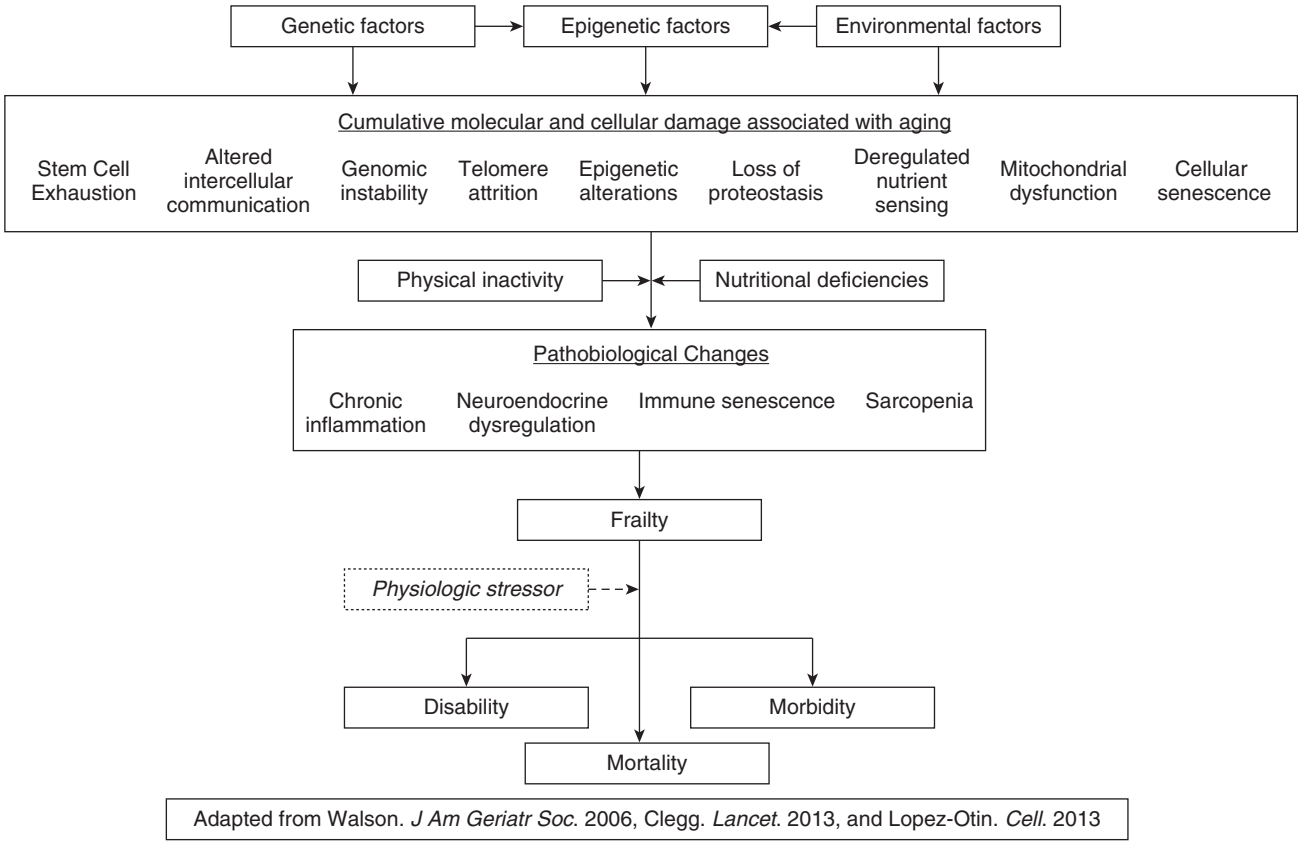

Figure 2. Hypothesized genetic, molecular, and functional changes underlying the frailty phenotype. Adapted by permission from References 18, 19, and 118.

muscle strength or function (29). The mechanisms by which sarcopenia develops include protein and micronutrient deficiencies, chronic inflammation, endocrine dysregulation, and disuse atrophy—all of which are also associated with frailty (30). Furthermore, certain biomarkers, such as IL-6 and TNF-α, directly induce muscle catabolism (31, 32).

Dysfunction in the endocrine axes affecting muscle metabolism is also associated with frailty. Frail adults have lower levels of insulin-like growth factor-1 (IGF-1), the signaling target of growth hormone and a key anabolic effector of muscle (25, 33–35). Sex hormones are lower in frail adults (i.e., estrogen in women and testosterone in men), as is 25-hydroxyvitamin D (25, 36–40).

Measurement of Frailty

Frailty is, by definition, a multidimensional syndrome (19). Not surprisingly, numerous instruments have been developed to operationalize its measurement, including clinician assessments, self-reports, physical performance assessments, or combinations of the three. Although numerous, they generally fall into two general models.

The first model considers frailty to be a biological syndrome, identifiable as a distinct phenotype. The Cardiovascular Health Study Index developed by Fried and colleagues (often referred to as the Fried Frailty Phenotype), is the most widely cited example of this model (2). The Fried Frailty Phenotype quantifies deficits in five domains: weakness (measured by hand-grip dynamometry), exhaustion (measured by responses to questions about effort and motivation) (41), shrinking (defined as unintentional weight loss $\geq$ 10 pounds in the last year), slowness (measured by gait speed over 15 ft), and low activity (ascertained by estimating kilocalorie expenditure) (42), with frailty being defined as deficits in at least three of these domains. Recent studies suggest that individual frailty domains have varying prognostic utility (43), with gait speed perhaps being the most discriminant predictor of incident disability and survival (44).

The second model, the cumulative deficit approach, defines frailty by enumerating abnormalities, with less attention paid to the specific nature of each problem or its severity. Rockwood and

Figure 1. (Continued). patients who are frail (*red line*) or not frail (*blue line*) prior to becoming critically ill. The thickness of the trajectory lines represents the proportion of patients in each trajectory. For a given insult, frail patients are susceptible to becoming critically ill sooner. Patients who are frail prior to critical illness are more likely to die in the hospital and more likely to develop chronic critical illness or severe disability leading to an early death. If they survive their critical illness, they are prone to recover functional status more slowly or develop permanent disability and a shorter lifespan than those who are not frail.

Table 1. Examples of instruments representative of the phenotype and cumulative deficit models of frailty

Instrument	Reference	Domains Assessed	Method of Frailty Domain Assessment	Populations Assessed	Scoring
Fried Frailty Phenotype (FFP)	Fried *et al.*, 2001 (2)	Nutritional status, physical activity, mobility, strength, and energy	Physical tests for slow gait and low physical activity and survey-based self-report assessment of weight loss, exhaustion, and weakness	Older adults aged ⩾ 65 yr	Range: 0–5; not frail: 0 frailty factors; prefrail: 1–2 frailty factors; frail: ⩾3 frailty factors
Short Physical Performance Battery (SPPB)	Guralnik *et al.*, 1994 (8)	Physical activity, mobility, strength, and energy	Battery of physical performance tests that include balance (tandem, semi-tandem, side-by-side), gait speed (4-m walk), and strength (sit to stand 5 times)	Older adults aged ⩾ 65 yr	Range: 0–12; not frail: ⩾10 points; prefrail: 8–9 points; frail: ⩽7 points
Study of Osteoporotic Fractures (SOF)	Kiely *et al.*, 2009 (119)	Nutritional status, mobility, strength, and energy	Self-reports of weight loss and reduced energy level and performance test of chair stands to assess weakness	Older adults aged ⩾ 70 yr	Range: 0–3; not frail: 0 frailty factors; prefrail: 1 frailty factor; frail: 2–3 frailty factors
Frailty Index/ Accumulation of Deficits	Rockwood *et al.*, 2006 (120)	Nutritional status, physical activity, mobility, strength, energy, cognition, mood, and social relations or social support	Enumeration of the total number of health deficits frequently affecting older adults out of a potential list of 70—presence or severity of diseases; deficits in activities of daily living; clinical and neurological problems	Older adults aged ⩾ 70 yr	Range: 0–70; higher score indicates more frail
Clinical Frailty Scale	Rockwood *et al.*, 2005 (10)	Nutritional status, physical activity, mobility, strength, energy, cognition, mood, and social relations or social support	Interview-based assessment and physician-assigned score of 1 (robust health) to 7 (complete functional dependence on others)	Older adults aged ⩾ 65 yr	Range: 0–7; not frail: score of 1–3; prefrail: score of 4; frail: score of 5–7

colleagues developed the two commonly used cumulative deficit frailty instruments: the Frailty Index and Clinical Frailty scale (3, 10). The original Frailty Index includes 70 clinical characteristics and laboratory measures believed to be associated with the development of adverse outcomes. Deficits in these 70 items are counted, and a Frailty Index score is then expressed as a ratio of the deficits present divided by 70. Because the assessment burden of the Index precludes its routine use in clinical settings, Rockwood and colleagues developed The Clinical Frailty Scale, a seven-point assessment tool wherein a clinician assigns a score on the basis of a patient's physical activity, social connectedness, burden of comorbidities, and cognition.

Although the phenotype and cumulative deficit models are operationally very different, both satisfy validity criteria and predict subsequent poor health outcomes in their target populations. Table 1 outlines some of the more extensively used frailty instruments. Additional instruments are outlined in Table E1 the online supplement.

Frailty in Pulmonary Disease

The associations between individual pathobiological and clinical constructs underpinning frailty and adverse outcomes in adults with lung disease are well described. For example, patients with COPD exhibit evidence of chronic systemic inflammation and endocrine dysregulation (assessed by biomarkers including IL-6, TNF, C-reactive protein, and IGF-1) compared with those without COPD (45–48). Furthermore, among those with COPD, higher levels of systemic inflammation biomarkers are associated with poorer physical function, exacerbations, and death (46, 49–51). Sarcopenia and cachexia are more common in patients with COPD than in matched healthy control subjects and are independently associated with reduced exercise capacity, functional performance, health status, readmission following hospitalization for acute exacerbation, and mortality (17, 46, 52–54). In addition, adults with COPD exhibit skeletal muscle dysfunction at the biochemical, cellular, and structural levels (13, 55–57).

Although most information is derived from those with COPD, a U.S. national registry study showed that lower 6-minute-walk distance is associated with mortality in adults with interstitial lung disease awaiting lung transplantation (58). In addition, lower preoperative 6-minute-walk distance and serum albumin (potentially reflecting malnutrition) is associated with mortality after lung transplantation across disease types (59, 60).

Identifying and Measuring Frailty in Patients with Lung Disease

Studies of frailty in adults with lung disease using validated instruments, however, are few and have focused on COPD or mixed populations of lung disease. Mittal and colleagues studied 120 patients with COPD, asthma, pulmonary fibrosis, or pulmonary arterial hypertension (61). The cohort was 18% frail (Fried Frailty Phenotype ⩾ 3), 64% prefrail (Fried Frailty Phenotype = 2), and 18% not frail (Fried Frailty Phenotype < 2). The prevalence of frailty

across lung disease types was not reported. Frail patients reported more frequent hospitalizations and falls than others. Frailty appeared to be associated with greater likelihood of hospitalizations: 76% of frail subjects, 60% of prefrail subjects, and 32% of not-frail subjects reported being hospitalized one or more times in the preceding year. A similar pattern was observed for falls. Notably, the authors defined "not frail" as meeting fewer than two criteria, whereas the more commonly accepted threshold defines "not frail" as meeting no frailty features. It is possible that the observed trends toward more hospitalizations and falls would have been greater if more commonly accepted thresholds had been used.

Lahousse and colleagues evaluated 2,146 community-dwelling older adults who completed Fried frailty assessments and spirometry (62). Of this group, 402 (19%) were diagnosed with COPD. Those with COPD were more likely to be frail than those without (10.2 vs. 3.4%; $P < 0.001$), and the severity of COPD appeared to be independently associated with being frail. After multivariable adjustment, compared with those without COPD, those with COPD without frequent exacerbations had 2.5-fold higher odds of being frail, and those with COPD and frequent exacerbations had 4.5-fold higher odds of being frail. Although the risk of death was similar in nonfrail patients with and without COPD, frail patients with COPD had a nearly threefold higher mortality rate than either of these two groups. Notably, frailty was a stronger predictor of mortality than was FEV_1% predicted or comorbidities.

Implications of Frailty in Patients with Chronic Lung Disease

In a study of 3,578 participants in the Cardiovascular Health Study, Vaz Fragoso and colleagues evaluated the relationship between a modified version of Fried's frailty instrument and respiratory impairments defined as either airflow limitation or restriction by spirometry (63). Participants completed a battery of assessments at baseline and at 4 years and had up to 12 years of vital status follow up. Prefrail and frail patients had 42% higher odds of developing respiratory impairments at follow up than those who were nonfrail, adjusting for relevant covariates. Conversely, after adjusting for the same factors, those with respiratory impairments at baseline had 58% higher odds of developing prefrailty or frailty at follow up than those without impairments. The impact of baseline respiratory impairments and frailty status on mortality appeared to be synergistic. Compared with nonfrail subjects with normal respiratory function, frail subjects with respiratory impairments had a nearly fourfold higher risk of death. This risk was at least twofold higher than that of nonfrail subjects with respiratory impairments or frail subjects without respiratory impairments.

Galizia and colleagues evaluated the impact of frailty on mortality in older adults with and without COPD (64). Subjects completed baseline assessments used to calculate the Frailty Staging System, a multidimensional count of deficits. Frailty was defined as mild, moderate, or severe. In those with COPD, 12-year mortality was 42% in nonfrail subjects, 53% in subjects with mild frailty, and 97% in subjects with severe frailty (test of trend $P < 0.001$). Each one-deficit increase in Frailty Staging System was associated with an 80% increased risk of death after covariate adjustment.

In a multicenter prospective cohort study, we evaluated the validity of the Fried Frailty Phenotype and Short Physical Performance Battery frailty measures in 395 candidates for lung transplantation with a mix of lung diseases (65). Among the cohort, 28% were frail by Fried Frailty Phenotype and 10% by the Short Physical Performance Battery. Frailty prevalence was similar across disease types. By either measure, worsening frailty scores were independently associated with increased disability. Furthermore, worsening frailty scores were independently associated with an increased rate of death or being removed from the wait-list because of clinical deterioration.

After covariate adjustment, each SD worsening in the Short Physical Performance Battery was associated with a threefold higher risk of death or delisting, and each SD worsening in the Fried Frailty Phenotype score was associated with a roughly 40% increased risk of death or delisting. Frail transplant candidates had protein biomarker evidence of systemic inflammation (higher levels of IL-6 and TNF-receptor 1), cachexia (lower levels of leptin), and aging (lower levels of IGF-1). The study is focusing now on whether preoperative frailty is associated with post-transplant complications, disability, and death.

In summary, frailty is independently associated with lower exercise capacity, disability, falls, hospitalizations, and mortality in adults with lung disease. Furthermore, the impact of lung disease and frailty on respiratory function and mortality appears to be synergistic, suggesting a more complicated relationship than simply one of comorbid conditions. These observations, particularly in patients with COPD, suggest that the mechanisms driving frailty outlined in Figure 2 (e.g., inflammation, endocrine dysfunction, muscle wasting) may also drive the progression of chronic lung disease and vice versa.

Frailty in Critical Illness

Older adults (aged $\geq$ 65 years) comprise about half of all intensive care admissions in high-income countries, receive more intensive treatments than in the past, and are more likely to survive critical illness than ever before (66, 67). Recognizing a need to identify those most suitable for palliative, rehabilitative, and therapeutic interventions (68, 69), investigators have begun examining frailty in older critically ill patients and survivors of critical illness.

Frailty on Admission to an Intensive Care Unit

In the largest study of frailty in critical illness to date, investigators measured the Clinical Frailty Score (10) at intensive care unit (ICU) admission in 421 adults aged 50 years or older across six hospitals. Defining frailty as a Clinical Frailty Score greater than 4, 33% were frail on ICU admission. Independent of age, sex, critical illness severity, and comorbidities, frail adults were twice as likely to die in the hospital (32 vs. 16%; adjusted odds ratio, 1.81; 95% confidence interval [CI], 1.09–3.01) and were twice as likely to die within 1 year (48 vs. 25%; adjusted hazard ratio, 1.82; 95% CI, 1.28–2.60). Frail adults were also more likely to be functionally dependent at hospital discharge and have lower health-related quality of life in the subsequent year (70, 71).

A multicenter prospective cohort study of 196 intensive care patients aged 65 years or older found similar independent associations between prehospitalization

frailty measured by Clinical Frailty Score and in-hospital and 6-month mortality (12). Investigators also measured prehospitalization frailty by the Fried Frailty Phenotype, although measurements of grip strength and walk speed were replaced with self- or proxy reports of mobility before critical illness that made the assessment possible in the ICU environment but may have compromised its construct validity. The modified frailty phenotype was independently associated with ICU, but not longer-term, mortality.

Frailty in Survivors of Critical Illnesses

The frailty deficits of undernutrition, weight loss, muscle wasting, and weakness that typically take years to develop in outpatient geriatric populations can develop or worsen rapidly in the critically ill, regardless of the specific critical illness diagnosis (68, 72). Therefore, measuring the Fried Frailty Phenotype domains in the heterogeneous population of survivors of critical illness may help posthospitalization outcome prognostication as well as identify potential deficits as therapeutic targets for intervention.

To date, one pilot study has demonstrated the feasibility of measuring Fried's frailty components in older medical survivors of critical illness after they were moved to the general ward. Once out of the ICU, they were usually able to answer questions and participate in dynamic assessments (73). Investigators modified certain Fried Frailty Phenotype domains to address measurement challenges in an ICU population: (*1*) those unable to walk were considered slow, (*2*) physical activity was based on leisure activities performed in the month before hospitalization, (*3*) feelings of exhaustion were assessed during the week before anticipated hospital discharge, and (*4*) next of kin answered questions if the subject was too debilitated to answer or could not remember. Using Fried's established cutoffs for each component and defining frailty as three or more deficits, 81% of older survivors of critical illness were frail. In unadjusted analyses, each 1-point increase in Fried frailty score was associated with a threefold increase in 6-month mortality (relative risk, 3.0; 95% CI, 1.4–6.3), and those with a score of 5 had an 83% 6-month mortality. A larger study to assess the independent association between post-ICU frailty and outcomes is ongoing.

These studies inform debates regarding the value of intensive care for older adults (67, 74, 75). Collectively, they suggest that older adults without frailty prior to critical illness may benefit most from intensive care, whereas those who are frail prior to critical illness are more likely to die in the hospital or are more likely to develop chronic critical illness or severe disability leading to early death (Figure 1B). These studies also highlight advantages and disadvantages with the cumulative deficit and phenotype approaches to frailty assessment. Cumulative deficit models may be most useful when frailty status needs to be known at ICU admission to screen patients into prospective cohort studies or trials or for retrospective studies that involve medical record review. Alternatively, phenotype models may be more useful for mechanistic studies that seek to understand the pathobiology of frailty in critical illness or as an outcome measure of response to interventions.

Biological Correlates of Frailty in Critically Ill Adults

In addition to clinical frailty assessments, investigators have examined biological components of frailty in critically ill adults, with a focus on muscle wasting and sarcopenia.

In a cohort of medical and surgical critically ill adults requiring mechanical ventilation, muscle wasting occurred rapidly during the first week of critical illness (76). Wasting was evidenced by a reduction in rectus femoris cross-sectional area measured by ultrasonography and decreased muscle protein synthesis and increased muscle protein breakdown measured by muscle biopsy. Low skeletal muscle mass, estimated by the cross-sectional area of muscle on abdominal CT scan, a previously validated measure of sarcopenia in older adults (77), is independently associated with in-hospital mortality in older trauma ICU patients and adults receiving mechanical ventilation (78, 79). These findings are consistent with prior studies in community-dwelling older adults showing low muscle mass increases the risk for subsequent disability and mortality (80–82).

Although a mild proinflammatory state (e.g., elevated TNF-α, IL-6) and decreased levels of anabolic hormones (e.g., IGF-1, dehydroepiandrosterone, testosterone) are associated with frailty in community-dwelling older adults (23, 35, 83, 84), these associations have not been evaluated in the critically ill or survivors of critical illness. However, two studies suggest that these associations may hold true in these populations as well. First, a study of older survivors of community-acquired pneumonia (14% of whom received ICU care) found that those with elevated levels of IL-6 and IL-10 within 48 hours prior to discharge had an increased risk of death over 1 year, independent of their severity of illness, age, and comorbidities (85). Second, a study that measured several hormones in critically ill subjects on the first day they regained consciousness following at least 7 days of mechanical ventilation showed that lower levels of IGF-1 and dehydroepiandrosterone were associated with in-hospital mortality (86).

Moving Forward

Refining Frailty Measurement in Pulmonary and Critical Care Medicine

It is likely that refinements to existing instruments may be needed for frailty assessment in lung disease and critical illness. Although existing instruments conceptually have face validity and the instruments described above have reasonable construct and predictive validity in lung disease and critical illness, none were developed specifically for these populations (2, 10). Some of the constructs, such as low activity or exhaustion in the Fried Frailty Phenotype, for example, may be confounded by lung disease or critical illness resulting in an overestimation of frailty. Furthermore, some single frailty constructs may explain the majority of the observed association between frailty and poor outcomes.

For example, slow gait speed is strongly associated with frailty and is also a powerful individual predictor of poor outcomes, including mortality—so much so that gait speed has been referred to as the "sixth vital sign" (43, 44, 87). Future work should focus on refining the operational measure of frailty in lung disease and critical illness through careful consideration of the measures used to assess theoretical constructs and validating the discriminant function and calibration of the overall instrument. Adding imaging or biomarker assessments may improve the instrument risk prediction.

Measurement of frailty in adults with lung disease has the potential to meaningfully affect clinical care. Frailty assessment may improve prognostication and explain functional limitations and disability that appear to be out of proportion to pulmonary impairment. Recent studies have shown that preoperative frailty and sarcopenia are associated with postoperative complications and mortality after major surgery (88–92). Measuring frailty in adults with lung disease preparing to undergo surgery—a group already at heightened risk for complications—could further improve risk stratification. Also, in lung transplantation, frailty assessment holds promise. Indeed, if frailty is associated with poor outcomes after transplant, preoperative assessment may identify patients unlikely to benefit from the intervention. If it is not, frail patients should be prioritized for organ allocation (93).

In those who are critically ill or have survived critical illness, frailty clearly identifies patients at greater risk for short- and longer-term dependency and mortality. Frailty assessment may therefore inform shared decision making about goals of care, particularly for older adults in the ICU (72). Second, assessing frailty before and immediately after critical illness may improve risk stratification and identify subgroups who may be most suitable for post-ICU palliative, rehabilitative, or therapeutic interventions. Indeed, better identification of survivors of critical illness at risk for persistent disability is needed in light of fact that three recent trials of post-ICU rehabilitation failed to detect a benefit, perhaps in part because too many survivors of critical illness, especially the young, recovered function with usual care, potentially diluting the treatment effect of rehabilitation (94–97).

Frailty as a Therapeutic Target in Pulmonary Disease and Critical Illness

Recent work in older populations shows that frailty may be reversible through targeted exercise and nutrition interventions (11, 98, 99). That muscle wasting, weakness, and malnutrition (hallmarks of frailty) are common in those with lung disease and should be responsive to physical exercise training and nutrition optimization underscores the importance of rehabilitation. Treating these frailty constructs may partially explain why pulmonary rehabilitation improves exercise capacity, disability, health-related quality of life, and, in COPD, reduces hospitalizations and mortality (100, 101).

Furthermore, if frailty is associated with postoperative complications in patients with lung disease, interventions aimed at reversing frailty could allow patients to undergo elective surgery in an optimized physical and nutritional state (i.e., "pre-habilitation"), potentially reducing postoperative complications, disability, and mortality (102). For lung transplant candidates, such interventions might reduce wait-list delisting or death as well as complications after transplant surgery. Notably, it is not clear whether the pathobiology causing frailty is universal across diverse lung diseases with heterogeneous pathophysiology or whether it differs by groups such as disease category underlying mechanisms (e.g., hyperinflammatory vs. sarcopenic or malnourished). Clarifying these questions could identify subgroups at differential risk for poor outcomes and inform tailoring of interventions.

In the ICU, our current evidence base suggests that we should first and foremost prevent frailty through minimizing sedation and through early mobilization, which have been shown to reduce ICU delirium as well as disability at hospital discharge (103). Further development and testing of novel rehabilitative therapies for critically ill patients and survivors of critical illness who are too weak to sit or walk is urgently needed (e.g., bedside cycle ergometry [104], neuromuscular electrical stimulation [105, 106]). Recent mechanistic research has begun to elucidate the molecular mechanisms of skeletal muscle dysfunction and wasting in aging and critical illness (76, 107, 108), which, in turn, has identified novel pharmaceutical targets to prevent muscle wasting and improve recovery of muscle function (e.g., ubiquitin proteasome system mediators [109], myostatin agonists [110]).

Prior efforts to treat the frailty deficits of undernutrition and endocrine dysfunction during critical illness underscores that caution must be exercised in differentiating between adaptive and maladaptive deficits. Trials to treat undernutrition during critical illness with supplemental nutrition have been ineffective and might have actually potentiated muscle atrophy and weakness (15, 76, 111–114), and a trial of growth hormone replacement in acutely critically ill medical and surgical patients doubled the risk of in-hospital death (115). In light of these studies, there is developing interest in targeting nutritional supplementation and hormone replacement therapies after ICU discharge to reverse weight loss and exhaustion in survivors of critical illness (116, 117).

Summary

Originally a geriatric construct, frailty is a generalized vulnerability to stressors resulting from an accumulation of physiologic deficits across multiple interrelated systems. Frailty is relatively common in subjects with lung disease and critical illness and is independently associated with poor functional status, exacerbations of lung disease, disability, poor health-related quality of life, and mortality. Assessing frailty may help clinicians identify patients at heightened risk for poor outcomes and those who may respond to targeted interventions. Multipronged efforts are needed aimed at refining clinical frailty assessments, understanding the mechanisms, and developing interventions targeting frailty in lung disease and critical illness that aim to preserve functional independence, reduce disability, and improve survival. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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