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Post-ICU Frailty: Does Critical Illness Accelerate Aging?

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Frailty is recognized as a leading cause of disability, hospitalization, institutionalization, mortality, and health care costs in older adults (1), but there is no consensus on how best to define and measure frailty (2). There are numerous valid measures of clinical frailty which can be classified under one of two main conceptual models (2): the frailty phenotype model (3), which defines frailty as biological syndrome that often occurs with but is distinct from disability or comorbidity, or the cumulative deficit model (4), which defines frailty by enumerating health related problems, with less attention paid to the specific nature of each problem. The Fried frailty phenotype (3), the most widely used phenotype measure, quantifies deficits in five frailty domains: weakness (measured by hand-grip strength); slowness (measured by gait speed over 15 feet); exhaustion (measured by responses to questions about effort and motivation); shrinking (defined as unintentional weight loss of 10 pounds in the prior year); and, low activity (ascertained from a validated questionnaire). Each frailty domain is assigned 1 point if present or 0 if absent based on established cutoffs (range, 0–5). Participants have been traditionally classified as robust (0 points), pre-frail (1–2 points) or frail (3 points). The most widely used measure of the cumulative deficit model is the Clinical Frailty Scale (CFS) (4), a 7-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. Traditionally, those with a score ≥ 5 are considered frail. Although the phenotype and cumulative deficit models are operationally different, they are both valid in identifying individuals at risk for adverse health outcomes both in geriatrics and critical care (5).

Over the past decade, the majority of studies in frailty and critical care have used the CFS instead of the frailty phenotype. Acutely critically ill patients cannot participate in frailty phenotype assessments. The CFS, which is largely based on a report of a patient's disability, mobility limitations, and comorbidities, can be easily assessed from the medical record and the patient's surrogate. Collectively, these studies have shown that approximately one third of all adults admitted to medical and surgical ICUs are CFS frail (6), with approximately one fifth of young and middle-aged adult patients being CFS frail (7, 8). These studies have shown that pre-hospital frailty is independently associated with in-hospital mortality, long-term mortality, and new nursing home admission after an ICU stay (6, 9).

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In the current issue of the journal, Brummel and colleagues add to the frailty critical care literature by being the first to provide prevalence estimates which suggest that hospitalization with critical illness accelerates the frailty process in adults of all ages. In a multi-center study consisting of nearly 600 patients, they longitudinally measured the CFS at hospital admission, and at 3 months and 12 months after hospital discharge. They show that 60% of survivors without prehospitalization CFS frailty are CFS frail at either 3 or 12 months after hospital discharge. Underlying this dramatic finding, however, is a median increase in CFS score of only 1 point between enrollment and 3-month follow-up, and enrollment and 12-month follow-up. The dichotomy between the large categorical increase in frailty and small increase in CFS score is explained by the fact that about half the cohort had CFS scores of 3 or 4, and thus many were already close to being frail at hospital admission. While these findings confirm those of landmark inception cohort studies of ARDS survivors that first identified deficits in 6-minute walk distance and limb strength that persisted for years (10, 11), the pre-admission to post-hospitalization increase CFS scores should help put to rest concerns that the deficits measured in inception cohorts of critical illness survivors represent predominantly unmeasured pre-hospitalization deficits.

Conceptually, these findings are quite intriguing. They suggest that physiologic deficits that may take years to develop in older adults develop or worsen within days in both younger and older ICU survivors, and then persist for up to one year. We know that common mechanisms governing age-related frailty are driven to extreme levels by critical illness. Most critical illness is associated with high levels of systemic inflammation (12), and subclinical inflammation is associated with accelerated declines in muscle mass, physical function, and frailty in older adults (13–15). ICU patients with prolonged critical illness have loss of the pulsatile secretion of anterior pituitary hormones (16), which results in extremely low levels of anabolic hormones in ICU patients (17, 18), and multiple anabolic hormone deficiency is associated with frailty in older adults (19). Mechanically-ventilated patients lose nearly 20% of their muscle mass during the first ICU week (20), and sarcopenia is inextricably linked with physical frailty in older adults. It was thus surprising that Brummel and colleagues found that the duration of sepsis (perhaps a surrogate of inflammation) and duration of mechanical ventilation (perhaps a surrogate for severe immobility) were not associated with clinically significant declines in CFS scores, especially since these are well-established risk factors for ICU-acquired weakness. These results could be confounded by death. Fifteen percent of the study cohort died between hospital discharge and 3-months, and an additional 15% of the cohort died between 3 and 12 months after hospital discharge. Perhaps those who had a longer duration of sepsis and mechanical ventilation were much more frail and died before follow-up. Bias from loss to follow-up among survivors seems unlikely. Loss to follow-up was low and the investigators used inverse probability weighting in their statistical models to account for attrition. The CFS score is judgement based, and intra- and inter-rater non-differential mismeasurement of CFS scores could bias associations towards the null. Lastly, if the observed lack of clinically meaningful associations is true, it suggests that we should measure critical illness risk factors for post-ICU frailty quite differently. Older adults who may be more susceptible to becoming frail may have less robust acute inflammatory and physiologic responses in sepsis, but more prolonged, chronic inflammation after sepsis (12). Duration of mechanical ventilation may contribute to post-ICU frailty only after many

days or when patients require deep sedation, since even mechanically ventilated patients with ECMO support can still be mobilized by specialized ICU physical therapy teams (21). Rather than studying the phenotypic characteristics of patients in the ICU, we should consider measuring longitudinally the dysregulation of primarily three systems affected by both critical illness and aging that are believed to underlie the development of frailty: (1) inflammation; (2) endocrine dysfunction; and (3), cellular energy production dysregulation (i.e. mitochondrial dysfunction) (22). Additionally, perhaps measuring the frailty phenotype in ICU survivors, and identifying the commonest domain deficits will elucidate which dysregulated systems drive post-ICU frailty.

By quantifying pre-admission and post-hospitalization frailty prevalence estimates in ICU survivors, Brummel and colleagues close the first chapter on frailty in critical care medicine research which has had an epidemiologic focus. They also suggest that we begin writing a new chapter with a mechanistic focus that seeks to elucidate the pathobiology of critical illness that drives post-ICU frailty, so that one day we may be able to prevent or even treat it.

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