Biological Mechanisms of Cognitive and Physical Impairments after Critical Care
Rethinking the Inflammatory Model?

There is a growing population of critical illness survivors who experience persistent impairments in physical, cognitive, and mental health outcomes. When assessed using detailed cognitive test batteries, almost two-thirds of survivors have substantial cognitive impairment at 12-month follow-up (1). Muscle weakness is also common and persistent after an ICU stay and is associated with impairment in physical functioning and health-related quality of life (2, 3).

Studies have identified clinical risk factors associated with these persistent impairments, but few large-scale studies have evaluated biological mechanisms (Figure 1) (1, 3). In preclinical studies, acute inflammatory biomarkers are associated with persistent cognitive impairment (4, 5) and muscle weakness (6). In critically ill patients, systemic inflammation has been associated with muscle weakness (7). Little is known, however, about the association between acute inflammatory responses and postdischarge cognitive and physical impairments (8). In this issue of the Journal, Brummel and colleagues (pp. 699–706) make an important contribution to the literature by evaluating the association between inflammatory and coagulation protein biomarkers with impairments in cognition and physical functioning at 3- and 12-month follow-up (9).

This study evaluates patients enrolled, from 2007 to 2010, into one of two multicenter, prospective cohort studies conducted at medical and surgical ICUs at five academic, community, and Veterans Affairs hospitals (9). The most common admission diagnostic categories of enrolled patients were sepsis (30%), surgical procedure (18%), cardiac (17%), and acute respiratory failure (16%), with a median interquartile range mechanical ventilation duration of 2 (1–6) days (9). Patients with preexisting cognitive impairment were excluded, and statistical analyses were adjusted for baseline physical function status, evaluated via survey-based measures. The following plasma biomarkers were quantified on Days 1, 3, and 5: CRP (C-reactive protein), IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, MMP-9 (matrix metalloproteinase-9), TNF-α (tumor necrosis factor α), soluble tumor necrosis factor receptor 1, and protein C. Separate regression models were used to evaluate the association between each biomarker and the following four outcome measures evaluated at 3 and 12 months: Repeatable Battery for the Assessment of Neuropsychological Status and Trail Making Test-Part B for cognition, and Katz Activities of Daily Living (ADL) Index and Functional Activities Questionnaire assessment of Instrumental ADL for physical function.

Of 630 survivors at 3-month follow-up, approximately 400–500 had full or partial outcome assessments at the 3- and 12-month time points. At both time points, cognitive test scores were approximately 1 SD below age-adjusted population means, and approximately one-fourth of survivors had physical disability. Notably, there was no association between any biomarker and cognitive test scores, but at both time points, higher levels of CRP and MMP-9 were associated with worse ADL and Instrumental ADL scores.

The study is notable for its large sample size with broad representation of ICU patients, and longitudinal capture of biomarkers early during critical illness. Furthermore, the measured biomarkers comprehensively evaluated dysfunctional inflammatory pathways that have been associated with adverse clinical outcomes in acute respiratory distress syndrome (ARDS) and sepsis. Moreover, statistical methods were used to help address potential bias from missing or incomplete outcome assessments.

Findings from this study suggest several areas for future research. First, the biomarkers in this population were only modestly elevated compared with more recent studies in patients with ARDS and sepsis (10). Hence, future studies should further refine patient eligibility criteria to select for those who may have a more robust inflammatory response. In addition, studies should further evaluate the association of CRP and MMP-9 with post-ICU physical outcomes because it was not possible to ascertain whether these markers have a specific mechanistic role or are merely a marker of disease severity, as the authors noted (9). The latter might manifest as an increased duration of mechanical ventilation and sedation, which may be associated with worse outcomes, independent of systemic inflammation. The duration of mechanical ventilation and the incidences of ARDS and sepsis were low in this study; therefore, some important risk factors for impairments may not have been fully captured.
Second, although several studies have documented the presence of elevated inflammatory biomarkers at discharge (11), few have evaluated biomarkers in the postacute setting, and even fewer have evaluated the association between such postacute biomarkers and subsequent impaired cognition and physical function (8, 11). In a study evaluating the association of inflammatory biomarkers and mobility at 3-month follow-up, CRP at 3 months, but not at ICU discharge, was associated with worse mobility at 3 months (12). Hence, studies are needed to evaluate the natural history of inflammation during and after critical illness to better understand survivors’ inflammatory profile.

Third, it is unclear whether the peripheral inflammatory biomarkers are a reflection of the inflammatory status of the brain. Ideally, studying inflammatory biomarkers in the cerebrospinal fluid could help advance our understanding of the pathophysiology of post-ICU cognitive impairment. However, such research is challenging to conduct in critically ill patients. Plasma biomarkers, such as S100B, have been proposed as markers of blood–brain barrier injury, and further evaluation of their temporal kinetics in ICU populations may yield additional insights into systemic inflammation, delirium, and long-term cognitive dysfunction (13).

Finally, other exposures throughout the continuum of care may alter the potential association between inflammation and subsequent physical and cognitive impairment. Such exposures include nutrition and physical and cognitive rehabilitation interventions. Bed rest is associated with increased inflammation, and exercise can enhance anti-inflammatory responses (14). Moreover, nutrition might mitigate the effects of inflammation and muscle loss in the ICU (14). Further research focusing on the potential synergistic effect of early rehabilitation combined with protein supplementation is underway (15) and may be important for better understanding the effects on inflammatory pathways and post-ICU impairments.

In conclusion, much progress has been made in understanding clinical risk factors for cognitive and physical impairments in critical illness survivors, but a great deal remains unknown regarding the pathophysiological pathways underlying such impairments. Future observational and interventional studies should further refine selection of ICU patient populations, evaluate biomarkers throughout the clinical continuum, and investigate the potential role of the blood–brain barrier, neuromuscular pathophysiology, and potential modifying effects of ICU care and relevant interventions to better understand and improve cognitive and physical impairments in survivors of critically ill patients.

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Ann M. Parker, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland
and
Outcomes After Surgery and Critical Illness Research Group
Johns Hopkins University
Baltimore, Maryland

Pratik Sinha, M.B. Ch.B., Ph.D.
Department of Anesthesia
Washington University
St. Louis, Missouri
Stuck in a Moment: Does Abnormal Persistence of Epithelial Progenitors Drive Pulmonary Fibrosis?

In idiopathic pulmonary fibrosis (IPF), a fibrotic niche is established that leads to persistent collagen deposition. The mechanisms underlying initiation and persistence of this niche and continuing progression of collagen deposition are poorly understood. In this issue of the Journal, Yao and colleagues (pp. 707–717) have developed a new mouse model of pulmonary fibrosis, induced by genetic Sin3a loss of function (Sin3a-LOF) in alveolar type 2 (AT2) cells (1). Unlike the single-dose bleomycin model of fibrosis, in which fibrosis peaks 21 days after exposure and then largely resolves, the fibrosis in Sin3a-LOF mice progresses steadily over 4–8 weeks, eventually causing death.

Yao and colleagues show that loss of Sin3a causes AT2 cells to adopt a complex cellular phenotype. The cells upregulate genes associated with hypoxia, mitochondrial dysfunction, DNA damage, and senescence. Similar patterns of gene expression were seen in single-cell sequencing of epithelial cells from patients with IPF. These cells expressed p21 protein and were hypoproliferative both in vivo and in organoids. Yao and colleagues further showed that the p53 pathway was critically downstream of Sin3a-LOF, as genetic and pharmacological p53 inhibition protected Sin3a-LOF mice from fibrosis. The persistence of dysfunctional epithelial cells was also critical to fibrosis, as a “senolytic” cocktail of dastinib and quercetin decreased the numbers of Sin3a-LOF cells and protected mice from fibrosis.

The transcriptional and functional phenotype of Sin3a-LOF cells has strong similarities to that of a recently described transient population of progenitor cells that emerges after various injuries, including bleomycin exposure, diphtheria toxin ablation, and Sepsis (MARS) Consortium. Increased early systemic inflammation in ICU-acquired weakness: a prospective observational cohort study. Crit Care Med 2017;45:972–979.

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