12. Marott JL, Ingebrigtsen TS, Çolak Y, Vestbo J, Lange P. Lung function trajectories leading to chronic obstructive pulmonary disease as predictors of exacerbations and mortality. *Am J Respir Crit Care Med* 2020;202:210–218.
13. Gladysheva ES, Malhotra A, Owens RL. Influencing the decline of lung function in COPD: use of pharmacotherapy. *Int J Chron Obstruct Pulmon Dis* 2010;5:153–164.
14. Lo Bello F, Hansbro PM, Donovan C, Coppolino I, Mumby S, Adcock IM, *et al*. New drugs under development for COPD. *Expert Opin Emerg Drugs* 2020;25:419–431.
15. Raghu G, Selman M. Nintedanib and pirfenidone: new antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions. *Am J Respir Crit Care Med* 2015;191:252–254.
16. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med* 2019;199:433–445.

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.

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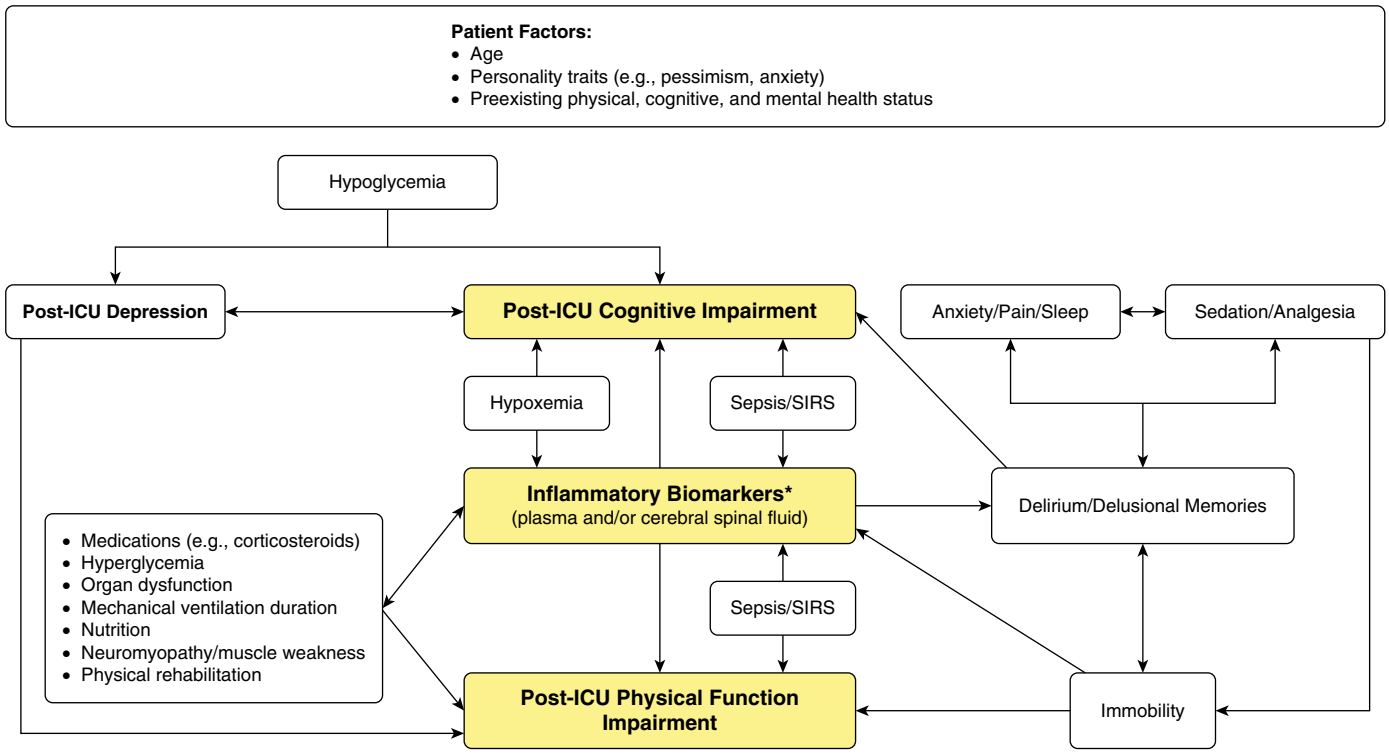

Figure 1. Proposed associations of inflammatory, patient, and hospital factors with cognitive and physical functioning impairments after critical illness. *Proposed temporal phases for studying inflammatory biomarkers: *1*) in-ICU (acute: up to Day 7; subacute: beyond Day 7), *2*) at discharge (ICU and hospital), and *3*) postacute (after hospital discharge). SIRS = systemic inflammatory response syndrome.

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 antiinflammatory 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 illness. ■

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References

1. Honarmand K, Lalli RS, Priestap F, Chen JL, McIntyre CW, Owen AM, *et al*. Natural history of cognitive impairment in critical illness survivors: a systematic review. *Am J Respir Crit Care Med* 2020;202: 193–201.
2. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, *et al*. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42:849–859.
3. Hopkins RO, Suchyta MR, Kamdar BB, Darowski E, Jackson JC, Needham DM. Instrumental activities of daily living after critical illness: a systematic review. *Ann Am Thorac Soc* 2017;14:1332–1343.
4. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care* 2019;23:352.
5. Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochem Soc Trans* 2011;39:945–953.
6. Fink H, Helming M, Unterbuchner C, Lenz A, Neff F, Martyn JA, *et al*. Systemic inflammatory response syndrome increases immobility-induced neuromuscular weakness. *Crit Care Med* 2008;36:910–916.
7. Witteveen E, Wieske L, van der Poll T, van der Schaaf M, van Schaik IN, Schultz MJ, *et al*.; Molecular Diagnosis and Risk Stratification of Sepsis (MARS) Consortium. Increased early systemic inflammation in ICU-acquired weakness; a prospective observational cohort study. *Crit Care Med* 2017;45:972–979.
8. Griffith DM, Vale ME, Campbell C, Lewis S, Walsh TS. Persistent inflammation and recovery after intensive care: a systematic review. *J Crit Care* 2016;33:192–199.
9. Brummel NE, Hughes CC, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, *et al*. Inflammation and coagulation during critical illness and long-term cognitive impairment and disability. *Am J Respir Crit Care Med* 2021;203:699–706.
10. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, *et al*. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* [online ahead of print] 16 Oct 2020; DOI: 10.1016/S2213-2600(20)30404-5.
11. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, *et al*.; GenIMS Investigators. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177: 1242–1247.
12. Griffith DM, Lewis S, Rossi AG, Rennie J, Salisbury L, Merriweather JL, *et al*.; RECOVER Investigators. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. *Thorax* 2016;71:820–829.
13. Blyth BJ, Farhavar A, Gee C, Hawthorn B, He H, Nayak A, *et al*. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J Neurotrauma* 2009;26: 1497–1507.
14. Heyland DK, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, *et al*. Combining nutrition and exercise to optimize survival and recovery from critical illness: conceptual and methodological issues. *Clin Nutr* 2016;35:1196–1206.
15. Heyland DK, Day A, Clarke GJ, Hough CT, Files DC, Mourtzakis M, *et al*. Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): a protocol of a multicentred, randomised controlled trial of combined cycle ergometry and amino acid supplementation commenced early during critical illness. *BMJ Open* 2019;9:e027893.

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

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