



Ⓔ No Strong Evidence for Ruling Out the Role of Coagulation in Long-Term Disability after Critical Illness

To the Editor:

We read with great interest the article by Brummel and colleagues regarding the role of inflammation and coagulation on long-term cognitive impairment and disability in patients with a critical illness (1). We congratulate the authors for their excellent work. Although the study provided solid evidence ruling out the influence of systemic inflammation on subsequent cognitive impairment and disability, the implications of activation of the coagulation system remain unclear. No direct markers of clotting activation were evaluated. Instead, the level of protein C, the zymogen precursor of activated protein C, was used as a marker of coagulation activation, as its circulating level is commonly decreased in systemic inflammation-associated prothrombotic states owing to its increased conversion to activated protein C (2, 3). However, it is unclear whether the levels of protein C were decreased in the population included in the study. Furthermore, besides its anticoagulant function, the beneficial effects of activated protein C under critically ill conditions (e.g., sepsis) are also attributed to its antiinflammatory, cytoprotective, and antiapoptotic activities that are mediated by the epithelial protein C receptor–dependent cleavage of the protease-activated receptor-1 (4, 5). Significant antiinflammatory actions of activated protein C include the suppression of the neutrophil extracellular trap formation, reduction of cytokine release from inflammatory cells, and protection of the endothelial barrier function (4–6). The insufficient information on the levels of protein C and the well-recognized anticoagulation-independent properties of protein C call into question whether protein C level was an appropriate marker for coagulation activation in the study. Circulating levels of more direct markers of coagulation system activation (e.g., D-dimer, activated factor V, or thrombin-antithrombin complex) would provide more informative results. On this basis, we believe that the data reported in the study are insufficient to rule out the effects of activation of the coagulation system on long-term disability after critical illness. ■

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References

1. Brummel NE, Hughes CG, 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.
2. Hazelzet JA. Levels of protein C and activated protein C: what do they mean? *Crit Care* 2006;10:126.
3. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. *Am J Respir Crit Care Med* 2020;202:361–370.
4. Christiaans SC, Wagener BM, Esmon CT, Pittet JF. Protein C and acute inflammation: a clinical and biological perspective. *Am J Physiol Lung Cell Mol Physiol* 2013;305:L455–L466.
5. Gabazza EC, Taguchi O, Suzuki K. Coagulation cascade: protein C and protein S. In: Laurent GJ, Shapiro SD, editors. *Encyclopedia of respiratory medicine*. Oxford, UK: Elsevier; 2006. p. 333.
6. Healy LD, Puy C, Fernández JA, Mitrugno A, Keshari RS, Taku NA, *et al*. Activated protein C inhibits neutrophil extracellular trap formation *in vitro* and activation *in vivo*. *J Biol Chem* 2017;292:8616–8629.

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Reply to Yasuma *et al*.



From the Authors:

We thank Dr. Yasuma and colleagues for their comments on our prospective multicenter cohort study “Inflammation and Coagulation during Critical Illness and Long-term Cognitive Impairment and Disability,” which evaluated the association between markers of acute inflammation and coagulation during critical illness with long-term outcomes in survivors (1). Several points are worthy of further discussion.

We agree that our study provides evidence that markers of acute systemic inflammation—which we measured only during the first week of critical illness—are not associated with longer-term cognitive and disability outcomes. Nevertheless, emerging data suggest that sepsis and other acute illnesses are a pathway by which some survivors of acute illness develop persistent inflammation (2). Given that higher levels of chronic inflammation have been associated with both cognitive impairment (3, 4) and disability (5, 6) in older adults without critical illness, the relationship between post-critical illness chronic

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inflammation and long-term outcomes in survivors of critical illness warrants further study (7).

As presented in Table E2 of our online supplement, the median (interquartile range) protein C activity (as a percent of control) in our study population was 80% (53–119%) on study Day 1, 88% (59–127%) on study Day 3, and 93% (64–137%) on study Day 5. Whereas the median levels of protein C activity in our cohort were higher than those reported in more homogeneous cohorts of patients with septic shock (8) or acute respiratory distress syndrome (9), a substantial number of participants in our study had mildly to moderately decreased protein C activity. Because lower levels of protein C activity are associated with greater mortality (10, 11), the relatively higher levels observed in our follow-up cohort may be attributable to the fact that our study included only those who survived at least 3 months following the index critical illness.

Finally, we also agree with Yasuma and colleagues that protein C is but one part of the complex coagulation cascade. Further study of the relationship between coagulation pathways and long-term outcomes in survivors of critical illness should be conducted. As with inflammation, evidence suggests that coagulation pathways can remain active after clinical resolution of acute illness and that higher levels of coagulation markers, such as D-dimer and thrombin-antithrombin complexes, at hospital discharge are associated with greater 12-month mortality (12). Thus, the longitudinal study of relationships between markers of coagulation with long-term outcomes in survivors of critical illness should be conducted (7). ■

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1. long-term cognitive impairment and disability. *Am J Respir Crit Care Med* 2021;203:699–706.
2. Yende S, Kellum JA, Talisa VB, Peck Palmer OM, Chang CH, Filbin MR, et al. Long-term host immune response trajectories among hospitalized patients with sepsis. *JAMA Netw Open* 2019;2:e198686.
3. Wichmann MA, Cruickshanks KJ, Carlsson CM, Chappell R, Fischer ME, Klein BE, et al. Long-term systemic inflammation and cognitive impairment in a population-based cohort. *J Am Geriatr Soc* 2014;62:1683–1691.
4. Windham BG, Simpson BN, Lirette S, Bridges J, Bielak L, Peyser PA, et al. Associations between inflammation and cognitive function in African Americans and European Americans. *J Am Geriatr Soc* 2014;62:2303–2310.
5. Cohen HJ, Pieper CF, Harris T, Rao KM, Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci* 1997;52:M201–M208.
6. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999;47:639–646.
7. Brummel NE. Long term outcomes of physical activity in older adults with critical illness. National Institutes of Health; 2016 [accessed May 5, 2021]. Available from: <https://reporter.nih.gov/search/1vFutA6RBkqivB34YtjobA/project-details/10130657>.
8. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al.; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
9. Ware LB, Matthay MA, Parsons PE, Thompson BT, Januzzi JL, Eisner MD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. *Crit Care Med* 2007;35:1821–1828.
10. Shorr AF, Bernard GR, Dhainaut JF, Russell JR, Macias WL, Nelson DR, et al. Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome. *Crit Care* 2006;10:R92.
11. Brunkhorst F, Sakr Y, Hagel S, Reinhart K. Protein C concentrations correlate with organ dysfunction and predict outcome independent of the presence of sepsis. *Anesthesiology* 2007;107:15–23.
12. Yende S, D'Angelo G, Mayr F, Kellum JA, Weissfeld L, Kaynar AM, et al.; GenIMS Investigators. Elevated hemostasis markers after pneumonia increases one-year risk of all-cause and cardiovascular deaths. *PLoS One* 2011;6:e22847.

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Nearby Neighborhoods with 25% Minority Residents Are Still Mostly White

To the Editor:

We applaud Borker and colleagues for bringing attention to the important subject of racial health disparities in the care of patients with obstructive sleep apnea (OSA) (1). Given the impact of OSA on overall health, disparities in OSA care can have massive societal health implications. The structural racism embedded in the healthcare system and in American neighborhoods that the authors highlight in the discussion is unquestionably an impediment to the health of Black and

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References

1. Brummel NE, Hughes CG, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, et al. Inflammation and coagulation during critical illness and