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.

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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