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Reply to Jain

From the Authors:

We thank Dr. Jain for his interest in our study (1). In his comment, he raises the issue of an alternate source of s-RAGE (soluble form of the receptor for advanced glycation end-products) in patients with coronavirus disease (COVID-19). More specifically, he suggests a key role of endothelial injury and ACE2 (angiotensin-converting enzyme 2)/ADAM17/TMPRSS2 pathway to explain baseline differences in levels of plasma s-RAGE between COVID-19–associated acute respiratory distress syndrome (CARDS) and non-CARDS. This could be of importance as this would suggest the role of systemic aggression in the morbidity and mortality associated with COVID-19 infection, may support a different pathophysiology of CARDS, and would limit the interpretation of s-RAGE as a marker of alveolar aggression in this subgroup.

As our study was not designed for that purpose, it is difficult to answer precisely to this assertion. However, Jain correctly points out some imbalance between CARDS and non-CARDS groups, which

could explain observed baseline levels differences, particularly through an endothelial production of s-RAGE.

First, we observed a higher prevalence of cardiovascular comorbidities in CARDS. We strongly agree that the level of soluble S-RAGE increases in inflammation, vascular dementia, diabetes, cardiovascular disease, and obesity. Nevertheless, in published data, s-RAGE remains below 1,000 pg/ml in these pathological conditions. In ARDS, plasma s-RAGE levels are between 3,000 and 4,000 pg/ml and bronchoalveolar samples show higher levels (up to 400,000 pg/ml) related to S-RAGE production by lung type 1 cells (2). It is therefore unlikely that the amount of s-RAGE related to comorbidities may have influenced our findings.

We agree that the AGE–RAGE axis is dysregulated in patients with diabetes or obesity, predisposing them to severe COVID-19 forms (3). If the cross-talk between Ang II/AT1R and RAGE after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could explain the pulmonary lesions observed in CARDS (increased lung capillary permeability and epithelial and endothelial damages), the predominance of endothelial lesions over pulmonary epithelial lesions in this context is not well established (4). From a clinical perspective, despite a high reported rate of thrombotic events (5), early mortality is mainly explained by refractory hypoxemia (78% in our cohort).

Second, Jain points out the lower proportion of severe ARDS in the CARDS group than the non-CARDS group, despite higher baseline s-RAGE levels suggesting that these results do not reflect increased lung epithelial injury. Our data did not support this assertion: when comparing s-RAGE levels in patients with mild ARDS, we did not observe any significant difference between patients with COVID-19 and patients without COVID-19 (median [interquartile range], 2,217 pg/ml [1,802–3,545] vs. 1,594.5 pg/ml [1,113.7–2,658.4]; $P = 0.277$). In contrast, s-RAGE levels were significantly higher in patients with COVID-19 with moderate or severe ARDS (data not shown). s-RAGE levels in both patients with COVID-19 and without COVID-19 significantly differed from control subjects (525.0 pg/ml [411.0–638.5]; $P < 0.001$) regardless of ARDS severity.

We believe that other factors could explain these differences. Several studies have reported that lung imaging patterns are associated with distinct profiles of lung injury biomarkers (including s-RAGE) during ARDS (6). We therefore compared s-RAGE levels according to lung morphology on imaging. Patients were classified as presenting focal pattern if areas of lung attenuation had lobar or segmental distribution, and nonfocal pattern if lung attenuations were diffusely distributed throughout the lung (7).

According to this definition, all patients with CARDS had a nonfocal radiological pattern. In patients with non-CARDS, 31 had focal and 86 nonfocal patterns. s-RAGE was significantly higher in patients with CARDS than those with non-CARDS with focal pattern (4,044.0 pg/ml [1,763.0–4,768.0] vs. 876.9 pg/ml [516.8–1,009]; $P < 0.001$) but did not differ from those with nonfocal pattern (4,044.0 pg/ml [1,763.0–4,768.0] vs. 3,074 pg/ml [1,933–4,375]; $P = 0.29$). Interestingly, taking into account radiological pattern, mortality was higher in patients with CARDS than in focal ARDS (adjusted hazard ratio, 2.58 [1.01–6.63]). This difference was not significant when compared with nonfocal ARDS (1.35 [0.77–2.35]).

In conclusion, we cannot rule out the possibility that s-RAGE levels in CARDS and non-CARDS may have been influenced by extrapulmonary epithelial factors, such as endothelium damages. If further studies are needed to determine the impact of such lesions, both lung imaging patterns and plasma s-RAGE levels suggest that lung alveolar edema and inflammation may be of paramount importance in the pathophysiology of CARDS. ∎

<u>Author disclosures</u> are available with the text of this letter at www.atsjournals.org.

Guillaume Dumas, M.D., Ph.D.*
Natacha Kapandji, M.D.
Elie Azoulay, M.D., Ph.D.
Hôpital Saint-Louis
Paris, France

Jean-Michel Constantin, M.D., Ph.D.
Sorbonne University
Paris, France
and

Hopital de la Pitié Salpétrière
Paris, France

On behalf of all the authors

*Corresponding author (e-mail: dumas.guillaume1@gmail.com).

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