


LETTER

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Lung compartmentalization of inflammatory biomarkers in COVID-19-related ARDS

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Dear Editor,

We read with great interest the article of Bendib et al. published in *Critical Care* [1], in which they systematically assessed inflammatory mediators in pneumonia-related ARDS, both in airways and blood compartments. The authors observed a lung compartmentalization of inflammatory mediators, with important heterogeneity in the bronchoalveolar lavage fluid-to-serum concentration ratios across the mediators screened. The concept of compartmentalization of inflammation has already been formulated in pneumonia [2], and issues raised by assessing lung inflammation using blood inflammatory markers has also been highlighted, as well as the subsequent limitations of these biomarkers for bedside management [3]. However, we believe that it is critical to examine it further in ARDS, in this COVID-19 era. Indeed, since the beginning of the pandemic, most of the studies exploring immune dysregulation during COVID-19 were nevertheless based on data obtained only from blood, not because this is the most relevant compartment, but because it is the most easily accessible.

In complement to the work of Bendib et al., we evaluated coincident inflammatory mediators in blood and respiratory fluids (endotracheal aspirates [ETA]) of 21 critically ill COVID-19 patients with ARDS requiring mechanical ventilation, within 48 h of their admission in ICU. As observed by Bendib et al., we found an

increased ETA-to-blood concentration ratio for IL-8, the cytokine for which concentration was the most compartmentalized to the lung. However, in our COVID-19 ARDS cohort, the median (quartile 1; quartile 3) ratio was highly elevated: 7355 (1959; 22433), compared to 20 in the study of Bendib et al. Moreover, ETA to blood concentration ratios of IL-1RA, IL-6, IFN- γ , TNF- α and CXCL10 were also highly elevated (Fig. 1), at a higher level than those reported by Bendib et al. for ARDS without shock. Thus, during COVID-19-driven ARDS -and even compared to non-COVID-pneumonia-related ARDS- inflammation appears highly compartmentalized to the lungs. These results are in line with publications reporting relatively low levels of systemic inflammatory mediators compared to other conditions requiring ICU [4, 5]. Taken together, these data challenge the concept of “systemic cytokine-storm” that has been employed to describe immune dysregulation during severe COVID-19. Consequently, in our quest of identifying reliable biomarker in pneumonia-induced ARDS -whether COVID or not-, lungs should not be excluded.

Authors' response

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Interleukin-8 is highly compartmentalized to the lungs in COVID-19 and non-COVID-19 ARDS

We thank Jouan et al. for their letter related to our recently published article [1]. Although serum

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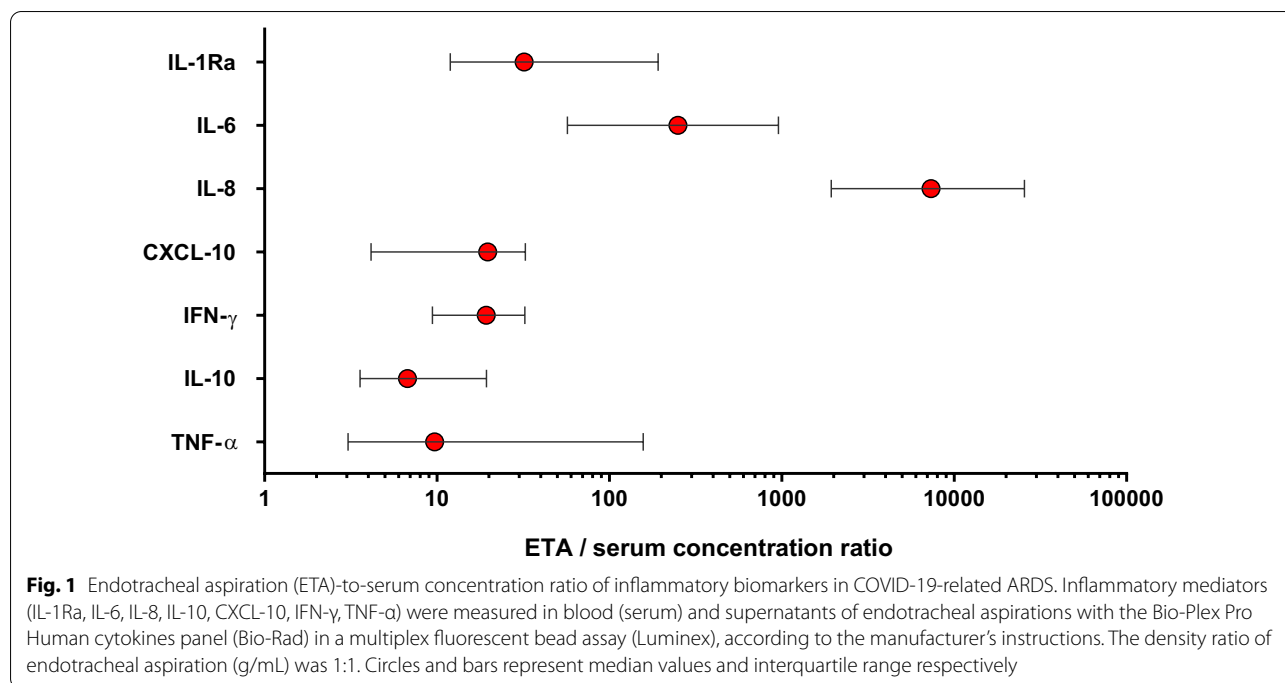
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biomarkers can depict specific profiles in patients with ARDS associated with COVID-19 and other diseases [6], the degree of cytokine release is markedly lower in critically ill COVID-19 than in other disorders associated with elevated cytokines (e.g., non-COVID-19 ARDS, sepsis, CAR-T cell therapy) [7]. Assessing the production of lung borne cytokines might thus be particularly relevant in COVID-19 patients. Consistent with our results in non-COVID-19 ARDS patients, Jouan et al. showed in patients with severe SARS-CoV-2 infection that the highest endotracheal aspirates (ETA) to blood concentration ratio was observed for interleukin-8 (IL-8). The authors pointed out some differences regarding the magnitude of the concentration gradient they measured (median value of the ETA to blood ratio of IL-8: 7355) and ours, which included only non-COVID-19 patients with pneumonia-associated ARDS (median value of the broncho-alveolar lavage (BAL) to serum ratio of IL-8: 21). Such magnitude difference might be due to the following factors: (1) a dilution of BAL fluid samples; (2) differences in IL-8 concentrations in proximal vs. distal airways and hypothetically, (3) higher IL-8 lung to blood concentration ratios in COVID-19 than in non-COVID-19 patients. ETA to blood concentration ratios of other cytokines, including interleukin-6 were also highly elevated in COVID-19 patients in the letter of Jouan et al. However, the clinical implications of these findings need to be investigated. Further studies will be needed to assess whether measuring lung to blood concentration ratios of selected biomarkers could help target patients most likely to benefit

from immunomodulating drugs targeting cytokine pathways [8].

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Authors' contributions

YG, TB, MST, CP and AG were involved in drafting the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed for this research letter are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All patients or their next of kin gave consent for participation in the study cited in this research letter. This work was part of an ongoing study exploring immune response during community-acquired pneumonia (ClinicalTrials.gov identifier: NCT03379207). The study was approved by the ethic committee "Comité de Protection de Personnes Ile-de-France 8" under the agreement number 2017-A01841-52, in accordance with the national laws.

Consent for publication

Not applicable.

Competing interests

No competing interests to declare.

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