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## **► To cite this version:**

Dara Chean, Samuel Benarroch, Frédéric Pochard, Nancy Kentish-Barnes, Élie Azoulay, et al.. Mental health symptoms are not correlated with peripheral inflammatory biomarkers concentrations in COVID-19-ARDS survivors. Intensive Care Medicine, 2022, <10.1007/s00134-022-06936-2>. <hal-03888549>

**HAL Id: hal-03888549**

**<https://hal.science/hal-03888549v1>**

Submitted on 9 Dec 2022

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# Mental health symptoms are not correlated with peripheral inflammatory biomarkers concentrations in COVID-19 ARDS survivors

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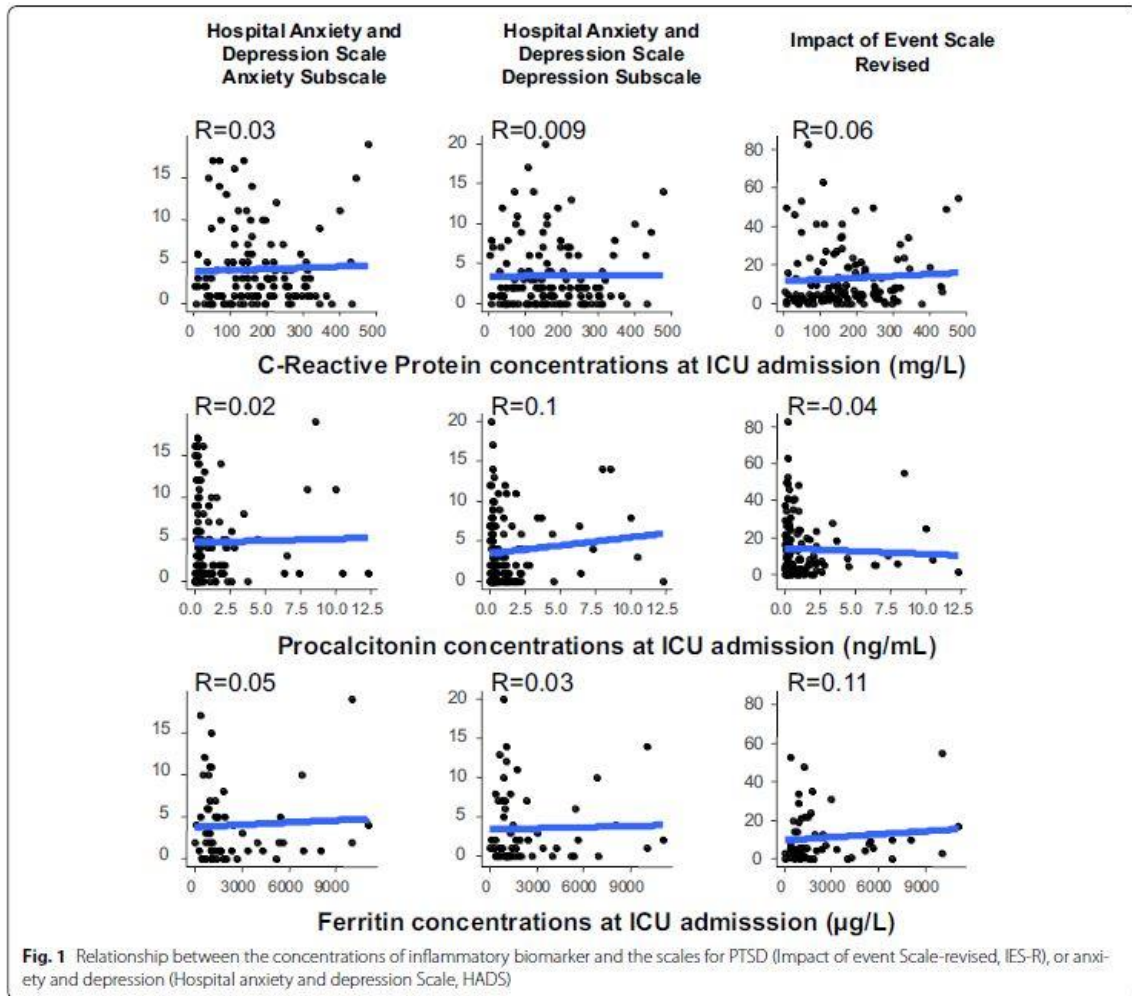
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Dear Editor,

Clinically significant and long-lasting symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD) are common in acute respiratory distress syndrome (ARDS) survivors [1]. Post-ARDS psychiatric morbidity is associated with younger age, female sex, prior psychological distress, unemployment, greater alcohol and opioid use, and the number of traumatic memories.

In patients survived after ARDS due to coronavirus disease 2019 (COVID-19), high levels of acute stress disorders have been reported [2]. Previous studies assessing mental health symptoms in ARDS survivors did not report any significant difference in the prevalence and the severity of PTSD-related symptoms between COVID-19- ARDS and other ARDS etiologies [3]. In general, studies of PTSD have consistently found increased concentrations of inflammatory cytokines and imbalances in immune cell proportions [4, 5]. Along this line, plasma concentration of C-reactive protein (CRP) has been associated with the development of PTSD symptoms in war zone-deployed Marines [4], with each tenfold increment in CRP concentration being associated with an odds ratio of PTSD symptoms of 1.51 (95% CI 1.15–1.97). However, in quarantined COVID-19 patients in whom very high rates of symptoms of anxiety and depression were self-reported [5], CRP concentrations and other inflammatory markers did not show statistical difference between patients with and without psychological symptoms.



Identifying patients at higher risk of mental health symptoms would offer the opportunity of preventive measures to avoid or alleviate the prevalence and severity of psychological burden. We sought to correlate peripheral inflammatory biomarkers to the development of symptoms of anxiety, depression and PTSD in critically ill patients with severe COVID-19 ARDS admitted to 23 intensive care units (ICUs) in France during the first COVID-19 wave (March and April 2020). These patients were reported elsewhere [3]. CRP, procalcitonin (PCT) and ferritin were sampled at ICU admission. During the day-90 telephone interviews, the patients completed the Impact of Event Scale Revised (IES-R) to assess PTSD-related symptoms and the Hospital Anxiety and Depression Scale (HADS) to assess the prevalence of symptoms of anxiety and depression. The Pearson correlation coefficient (R) was used to measure the strength and the direction of the linear relationship between the concentrations of inflammatory biomarker and the IES-R, or the anxiety and the depression subscales of the HADS.

Among the 178 ICU patients with COVID-19 ARDS, assessment of mental health symptoms was available in 156 (88%, median age 59 (IQR 50–68), 118 (76%) men and 38 (24%) women). Mechanical ventilation was required in 114 (73%) patients and 42 (27%) required high flow nasal oxygen only. Symptoms of anxiety (HADS-anxiety subscale > 7), depression (HADS-depression subscale > 7), and PTSD (IES-R > 22) were found in 25%, 22% and 22% of the patients, respectively. Symptoms of anxiety and depression were found in 55% and 42% of patients with PTSD, respectively, as compared to 9% and 8% of patients without PTSD, respectively. CRP concentration at admission was 157 mg/l (IQR 86–246), procalcitonin was 0.37 ng/ml (0.16–1.17), and ferritin was 1280 µg/l (830–2605). Pearson correlation coefficient for the association between CRP and the anxiety subscale of the HADS was 0.03, showing a poor association between the two scores (Fig. 1). Similar figures were found for the association between CRP and the depression subscale of the HADS or the IES-R ( $R = 0.009$  and  $R = 0.06$ , respectively). Similarly, PCT concentrations at admission were poorly correlated with the anxiety or depression subscales of the HADS or with the IES-R ( $R = 0.02$ ,  $R = 0.1$ , and  $R = -0.04$ , respectively). Last, ferritin concentrations at admission were also poorly correlated with mental health symptoms ( $R = 0.05$  for the anxiety subscale of the HADS,  $R = 0.03$  for the depression subscale of the HADS, and  $R = 0.11$  for the IES-R).

In conclusion, peripheral inflammatory biomarkers are poorly correlated with further occurrence of symptoms of anxiety, depression or PTSD in survivors of COVID-19 severe ARDS. Until PTSD-specific biomarkers can be identified validated in this setting, early screening of mental health symptoms in ARDS survivors should be offered regardless the concentrations of initial peripheral inflammatory biomarkers.

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### **Acknowledgements**

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### **Funding**

All financial support for the research was provided by the French Ministry of Health (Grant COVID2020).

### **Declarations**

#### **Conflicts of interest**

Authors declare no conflict of interest in relation with this manuscript.

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