## Réanimation respiratoire : translationnel

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# Association between volume of lung damage and endoplasmic reticulum stress expression among severe COVID-19 ICU patients

D. Renard*(1), . Verdalle-Cazes (2); P. Leprêtre,(1,3); J. Bellien,(3,4), V. Brunel (5); S. Renet(3); F. Tamion,(3,6), E.Besnier (1,3), T. Clavier (1 ,3)

(1) Anesthésie Réanimation, CHU Charles Nicolle, Rouen, France, (2) Department of Radiology, CHU Rouen, F-76000 Rouen, France., (3) INSERM EnVI UMR 1096, University of Rouen Normandie, F-76000 Rouen, France, (4) Department of Pharmacology, CHU Rouen, F-76000 Rouen, France, (5) Department of General Biochemistry, CHU Rouen, F-76000 Rouen, France, (6) Medical Intensive Care Unit, CHU Rouen, F-76000 Rouen, France.

**Auteur présenté comme orateur*

**Position du problème et objectif(s) de l'étude:**
Links have been established between SARS-CoV-2 and endoplasmic reticulum stress (ERS). However, relations between inflammation, ERS and organ damage are little known by humans. A recent sudy suggested that inflammation was little associated with tissue trauma but driven by infection while ERS was essentially driven by tissue trauma more than by infection or systemic inflammation. Our aim was to explore association between ERS and lung damage volume (LDV) among COVID-19 patients admitted in ICU.

**Matériel et méthodes:**
We conducted a single-center retrospective study (ancillary analysis of a prospective cohort) including severe COVID-19 ICU patients hospitalized in three ICU of a tertiary care hospital between May and November 2020 that have had a chest computer tomography (CT) 24 hours before/after admission to assess LDV.
This cohort was approved by an ethics committee (Comité de Protection des Personnes Est-III, approval number 2020-A00885-34). According to the French law, verbal approval was required from the patient or their relatives.
Blood was collected on ethylenediaminetetraacetic acid tubes within the first 24 hours after ICU admission.
CT scans were reviewed by a single radiologist blinded to the patient's condition and biologies. We performed two multivariate linear regression models looking for factors associated with plasma levels of 78kDa-Glucose-Regulated Protein (GRP78; ERS marker) and Interleukin-6 (IL-6; inflammation marker) at admission.

**Résultats & Discussion:**
Among 63 patients analyzed, GRP78 was associated with LDV in both multivariate models (β=22.23 [4.08;40.38]; p=0.0179, β=20.47 [0.74;40.20]; p=0.0423) but not with organ failure (Sequential Organ Failure Assessment (SOFA) score) at admission (r=0.03 [-0.22;0.28]; p=0.2559). GRP78 was lower among ICU survivors (1539.4 [1139.2;1941.1] vs. 1714.2 [1555.2;2579.1] pg/mL. respectively; p=0.0297). IL-6 was associated with SOFA score at admission in both multivariate models (β=136.60 [65.50;207.70]; p=0.0003, β=193.70 [116.60;270.90]; p<0.0001) but not with LDV (r=0.13 [-0.14;0.39]; p=0.3219). IL-6
levels were no different between ICU survivors and non-survivors (12.2 [6.0;43.7] vs. 30.4 [12.9;69.7] pg/ml. respectively; p=0.1857). There was no correlation between GRP78 and IL-6 (r=0.13 [-0.13;0.37]; p=0.3106).
Among severe COVID-19 patients, ERS was associated with LDV but not with systemic inflammation, while systemic inflammation was associated with organ failure but not with LDV.

**Conclusion:**
Our results suggest that ERS could be independently associated with the volume of lung damage in severe COVID-19 patients. We did not find any association between GRP78 and inflammation or systemic organ failure. IL-6 seemed independently associated with systemic organ failure but not with tissue damage. Finally, the IL-6 level was more correlated with
short-term severity while GRP78 level was associated with short-term mortality. We developed two

models of multivariate analysis for GRP78 and IL-6 levels. One with strictly associated parameters in univariate analyses, the second one taking into account relevant factors found in the literature. The aim was to take into account as many confounding factors as possible, including those not found in our study and to strengthen the value of our findings with a "double methodology".
Given ERS association with organ damage, it would be interesting to study its relationship with long-term functional outcome among COVID-19 patients.

**Références bibliographiques:**
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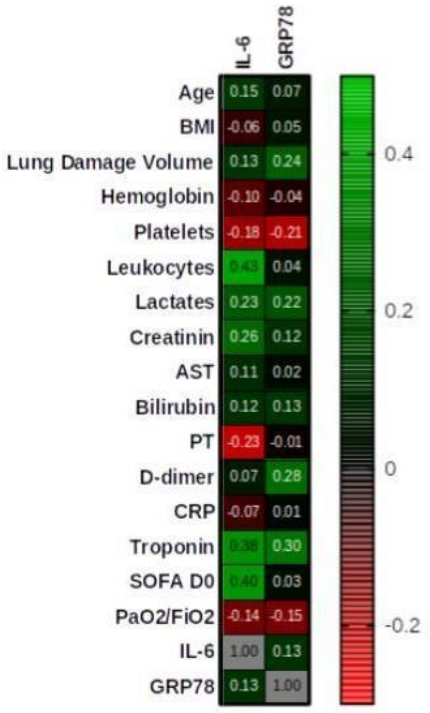


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