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Presence and evolution of NET markers and DAMPS in critically ill COVID-19 patients

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Background: The coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection presents with a wide range of disease symptoms. In the more severe patients, COVID-19 is associated with respiratory failure, neutrophil extracellular trap (NET) formation, and multiple organ failure (MOF).
Aims: We investigated the presence and evolution of several damage associated molecular patterns (DAMPs) neutrophil markers and immune modulators in a group of 100 COVID-19-positive ICU patients.

Methods: Citrated plasma was collected from adult patients with confirmed COVID-19 by PCR detection of SARS-CoV-2 E and N-genes in nasopharyngeal swabs admitted to the intensive care unit (ICU) at Uppsala University hospital, Sweden. Written informed consent was obtained from the patients, or next of kin if the patient was unable to give consent. The Declaration of Helsinki and its subsequent revisions were followed. Plasma concentration of cell free DNA (cfDNA), extracellular histone H3 (H3), neutrophil elastase (NE), myeloperoxidase (MPO) and the cfDNA-MPO complex, and the immune modulators GAS6, and sAXL were measured in all COVID-19-positive and in COVID-19-negative patients and healthy controls. We determined marker levels upon admission, of their evolution, and correlation with disease severity, organ failure, thromboembolic events, mortality, and other blood parameters.
Results: The level of cfDNA, H3, NE, MPO, cfDNA-MPO complex, GAS6, and sAXL were all significantly increased in plasma of COVID-19 patients compared to controls. Importantly, a diminution of cfDNA and GAS6 levels over time was observed in patients surviving 30 days after ICU admission. Histone H3 levels were detected in 40% of the COVID-19 patient plasma at ICU admission and the presence of histone H3 during ICU stay was associated with an increased risk of thromboembolic events and secondary infection. Though NET markers were not predictive of 30-day mortality, they correlated with several parameters of tissue damage and neutrophil counts.
Summary/Conclusion: The increased presence of cfDNA, H3 and NE, MPO, and MPO-DNA illustrates the severity of cellular damage and indicates activation of NETosis in severe COVID-19 ICU patients. The evolution of cfDNA and Gas6 is able to predict disease prognosis of severely ill COVID-19 patients, where GAS6 appears to be part of an early activated mechanism in response to COVID-19. These data support treatment aimed at the reduction of NET formation in severe COVID-19 patients.