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# Plasma calprotectin levels are increased in COVID-19 patients and correlate with other biomarkers and conditions associated with severe form of the disease

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## INTRODUCTION

The 2019 coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus has heterogeneous clinical appearances, from asymptomatic and mild to severe form of the disease. Dysregulated immune response characterized by cytokine storm, increased neutrophil count and infiltration of the neutrophils in the lungs are observed in patients with severe COVID-19. Elevated levels of blood neutrophils have been reported to associate with poor oxygenation in COVID-19 patients. Calprotectin is a major protein in the cytosol of neutrophils and is rapidly released upon neutrophil activation. Calprotectin has been suggested as a mediator of the inflammatory response and an early biomarker for prediction of the disease severity in COVID-19 patients. The aim of the present study was to evaluate performance of calprotectin in prediction of the disease severity in COVID-19 patients admitted to the ICU.

## METHODS

121 patients admitted for COVID-19 infections to the intensive care unit (ICU) at Uppsala University Hospital were included in this observational study. 11 preoperative patients admitted to the same ICU for cytoreductive surgery with peritoneal carcinosis were used as controls. Analysis of calprotectin was performed in plasma with particle enhanced turbidimetric assay (Gentian AS, Moss, Norway) on Mindray BS200 instrument. D-dimer, TPK, CRP, Lactate and Ferritin analyses were performed in the hospital central laboratory as a standard of care. Lung function analysis by PaO2/FiO2 ratio and blood lactate by arterial blood gas was recorded on admission to ICU. Analysis of e-selectin was performed by ELISA (DY724, R&D Systems, Minneapolis, MN, USA). Critical illness weakness is defined as ENG/EMG diagnosed polyneuromyopathy.

## RESULTS

Calprotectin in plasma was significantly increased in COVID-19 patients compared to the control group of preoperative cancer patients admitted to the ICU prior to the COVID-19 outbreak. Calprotectin levels differentiated between COVID-19 and non-COVID-19 patients with an area under the curve of 0.991 according to the ROC analysis. Positive correlation was observed between levels of calprotectin and other inflammatory and hypoxic biomarkers such as CRP, Ferritin, D-dimer, Lactate and negative correlation to gaseous exchange as measured by PaO2/FiO2.
Calprotectin positively correlated with e-selectin, a biomarker for endothelial cell damage and with ICU acquired weakness that develops in the setting of critical illness.

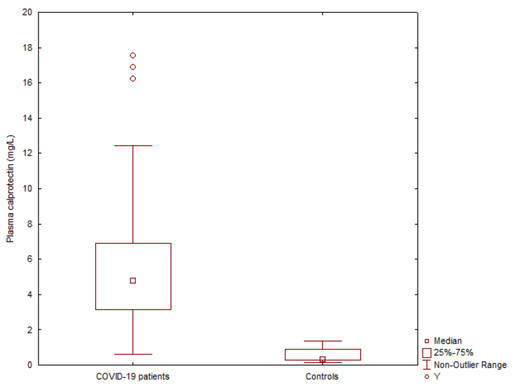
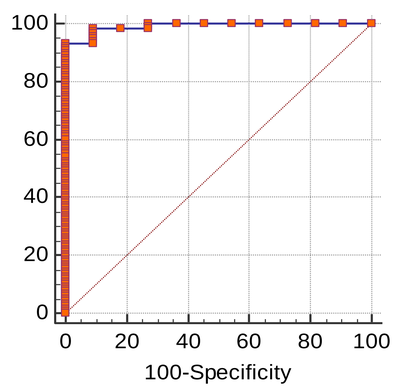



Fig 1. Calprotectin levels in COVID-19 patients and controls

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|---|---|
| AUROC | 0,991 |
| Sensitivity | 93,22 |
| Specificity | 100,00 |
| P-value | < 0.0001 |

Fig 2. ROC curve for differentiation between COVID-19 and Non-COVID-19 patients admitted to ICU

## CONCLUSION

Concentration of calprotectin in plasma is significantly elevated in ICU-treated COVID-19 patients, confirming the involvement of neutrophils and presence of an inflammatory cascade. As the release of calprotectin is very rapid in response to neutrophil activation, calprotectin has been suggested as an early marker for differentiation between mild and severe form of the disease and valuable tool for risk stratification in severe COVID-19. Calprotectin levels correlated with other inflammatory and hypoxic biomarkers as well as with e-selectin indicating a potential role of calprotectin in prediction of damage of endothelial cells and subsequent organ failure. Moreover, observed correlation with critical illness weakness suggests the role of calprotectin in systemic inflammation causing the ICU acquired weakness in critically ill patients.

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