

## Time-resolved plasma proteomics predicts survival outcome of COVID-19 patients during hospitalization

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The need to understand the progression of COVID-19 and SARS-CoV-2 infection is essential to identifying potential biomarkers and therapeutic targets. Monitoring the progression of the disease is essential to predict the prognosis of patients from the initial times of hospitalization. The goals of this study are to comprehend the trajectory of the disease by characterizing changes in the plasma proteome over time and propose putative biomarkers proteins that can differentiate between non-survivor and survivor phenotypes. During hospital admission, plasma samples were collected weekly from 44 unvaccinated patients over a six-week period from Hospital de Clinicas de Porto Alegre Biobank (total = 198). Plasma was processed using S-Trap™ digestion protocol and acquired in 90 min gradient using a Vanquish™ Neo UHPLC System coupled to an Orbitrap Exploris™ 480 Mass Spectrometer. Proteins were identified using DIA-NN software. Proteomics analysis identified a total of 1600 proteins, of which 851 were selected for quantitative analysis. It was observed that the acute phase response and the inflammatory reaction was dysregulated over time returning to normal levels by the sixth week. Other processes such as antigen binding, endocytosis, and vesicle-mediated transport increased during hospital admission related to the first week. In the global correlation map was observed clusters associated with cytokine stimulation, insulin-like growth factor II binding, complement cascade and acute-phase response. Furthermore, the comparison between patients who survived and those who died revealed differentially abundant proteins even in the first weeks of hospitalization. In non-survivor patients were found more abundant proteins related to complement activation and the innate immune response, while the humoral response and antibody-related annotations decreased in these patients, especially in the first three weeks. From the fourth week onwards, patients who died related to survivors present increased acute inflammatory response, accompanied by a reversal of previously diminished processes, such as leukocyte chemotaxis and complement activation. To identify potential biomarkers that could predict survivor or non-survivor phenotypes a linear SVM model was trained with proteins with different statistical significance HPR, PF4, LPA, IGFALS, COLEC11 resulting in a ROC curve with AUC 0.916. In addition, the model correctly classifies 85% of the patients. This study provides insights into the pathophysiology and progression of COVID-19 and highlights proteomics as a powerful tool for understanding the host response during viral infection as well as correlating and validating the clinical information

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