V08 Early multi-omics immune correlates of severe versus asymptomatic COVID-19 disease

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Background and objectives: COVID-19 patients present a versatile range of severity from asymptomatic to debilitating symptoms and critical conditions requiring hospitalization. To understand the viral and immune correlates of severity, we investigated multiple dimensions of the immune response, including single cell proteomics, early after a SARS-CoV-2 (SCV2)-positive test. Materials and methods: Patients (N = 174) were recruited early after their first SCV2-positive test, and 4 samples were taken within the first month. Serum cytokine levels by ultra-sensitive ELISA (Simoa, Quanterix) and SCV2 viral load (RNA and nucleocapsid antigen) were measured. PBMCs were analyzed by singe-cell intra-cellular-staining (ICS) cytometry and single-cell CyTOF, before and after stimulation with spike and nucleocapsid peptide pools. Bioinformatics analysis (PCA, UMAP, and ML) was performed to cluster the patient groups and identify the cellular immune correlates. Results: A cyto-

kine combination, based on the ratio of inflammatory cytokines to type-I interferons, was identified as a highly accurate (> 95%) early predictor of both the likelihood for hospitalization and symptom severity, already at the day of PCR testing. Moreover, asymptomatic patients present with significantly lower viral loads and cytokines, in correlation with higher frequencies and counts of SCV2-specific activated CD4 and CD8 T cells. In particular, asymptomatics show a significantly higher frequency of Th1-related cytokine expression, and of note a higher level of poly-functional CD4 and CD8 T cells expressing multiple cytokines. Interestingly, asymptomatic status is more significantly associated with a potent response against nucleocapsid antigen, rather than against spike antigen. Conclusions: COVID-19 hospitalization and symptom severity can be accurately predicted already at the first positive test. This early predictor, which is feasibly measurable at point-of-test setting, can guide personalized medicine with anti-viral or cytokine inhibitor therapy. Furthermore, single-cell analysis allowed us to identify the immune correlates behind this predictor. Asymptomatic disease course is characterized by a potent anti-nucleocapsid CD4 and CD8 Th1 response, associated with lower inflammatory cytokine levels. These results have important clinical relevance for the development of both personalized therapy and vaccines aimed at reducing severity, by indicating the correlates of asymptomatic disease course.