**Objective** COVID-19-associated pulmonary aspergillosis is a well-known respiratory superinfection with *Aspergillus* spp. in critically ill COVID-19 patients. Despite rapid diagnosis and prompt initiation of antifungal treatment, mortality remains unacceptably high. Novel non-invasive diagnostic and prognostic biomarkers for CAPA are currently lacking.We aimed to identify early circulating host inflammatory proteins for CAPA using proximity extension immunoassays on blood samples taken during the first week of ICU stay and explore their prognostic potential in CAPA patients.

**Methods** In this two-center international cohort of critically ill COVID-19 patients, EDTA plasma samples were prospectively collected during the first week of ICU admission and stored at −80°C. Ninety-two inflammation-related protein biomarkers were quantified using multiplex proximity extension immunoassays (Olink Target 96 Inflammation panel). Differentially expressed proteins (DEPs) between CAPA survivors and non-survivors were assessed using Mann–Whitney U tests on normalized protein expression (NPX) values with Benjamini–Hochberg correction for multiple testing. Pairwise Spearman correlation coefficients were computed and visualized via correlograms, with hierarchical clustering (median linkage) for term ordering. Pathway enrichment analysis was performed using ClueGO (Cytoscape plugin) based on Gene Ontology (GO) Biological Process terms.

**Results** Plasma samples were collected from 77 critically ill COVID-19 patients at a median of 3 days since ICU admission (IQR 2 – 6). CAPA incidence was 38% (29/77). All patients underwent invasive mechanical ventilation and received corticosteroids. 30-day mortality was 34% (10/29) in CAPA and 21% (10/48) in COVID-19-only patients (p = 0.2). Differential expression analysis revealed limited differences in protein expression patterns between CAPA and COVID-19 only patients. However, in CAPA patients specifically, we identified 20 downregulated proteins in deceased patients (n = 10) vs. surviving patients (n = 19), 3 of which remained significant upon correction for multiple testing (IL12B, TNFB, uPA) (Figure 1A). Significant correlations were observed between IFN-gamma, IL12B and TNFB, among others (Figure 1B). Lastly, pathway enrichment analysis on the downregulated DEPs in deceased CAPA patients showed downregulated pathways involved in T cell activation and differentiation (Figure 2).

**Conclusions I**n this proof-of-concept study, we identified early downregulation of several circulating inflammatory proteins involved in T-cell functioning in non-surviving CAPA patients, suggesting a critical role for the adaptive immune response in controlling invasive fungal infection in critically ill patients with virus-associated pulmonary aspergillosis. Our findings warrant prospective multicenter validation, also in IAPA patients, to fully elucidate the potential of circulating proteins as prognostic marker and targets for adjunctive personalized immunotherapy.