

ELECTRONIC SUPPLEMENTARY MATERIAL 1

Key factors of the deranged antiviral response in elderly patients with COVID-19: a machine-learning analysis

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Supplementary Text S1 Pg 5

Protein–protein interaction network and functional pathway enrichment analysis

Protein-protein interactions and functional enrichment analysis were performed using STRING (version 12.0; <https://string-db.org/>), Cytoscape (version 3.10.4), and Enrichr (<https://maayanlab.cloud/Enrichr/>). Fold change for each protein plasma concentration was calculated as the median protein concentration in the elderly group divided by the median protein concentration in the adult group. Protein-protein interactions network plot was obtained with STRING, providing official gene names representing each protein and their associated $\log_2(\text{fold-change})$.

Proteins that reported the greatest importance in the machine learning analysis were grouped according to their SHAP value sign associated to elderly host response. Functional enrichment analysis was performed to determine the pathways, biological processes, molecular functions, and diseases, among others, that were significantly overrepresented in each group of proteins. STRING results were transferred and extracted from Cytoscape and confirmed with Enrichr. To control the false discovery rate in multiple hypothesis testing it was used the Benjamini-Hochberg method.

For this section, Tissue Factor (TF, F3) was used as a surrogate marker of the procoagulant state reflected by D-dimer plasma concentrations since it is not possible to include D-dimer in these tools and being aware of the biological rationale with its limitations. TF triggers coagulation cascade activation resulting in fibrin clot formation necessarily for D-dimer generation and experimental data have shown significant correlations between TF and D-dimer levels in COVID-19 (PMIDs: 34377969, 27886531, 32367170, 33824483, 30633597, 32685883).