Prognostic tools and candidate drugs based on plasma proteomics of patients with severe COVID-19 complications

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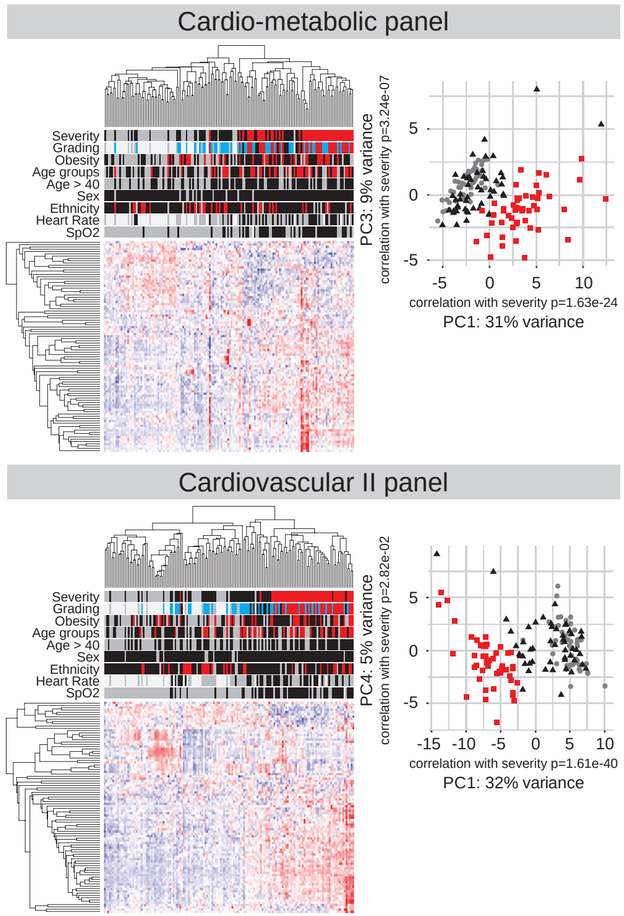
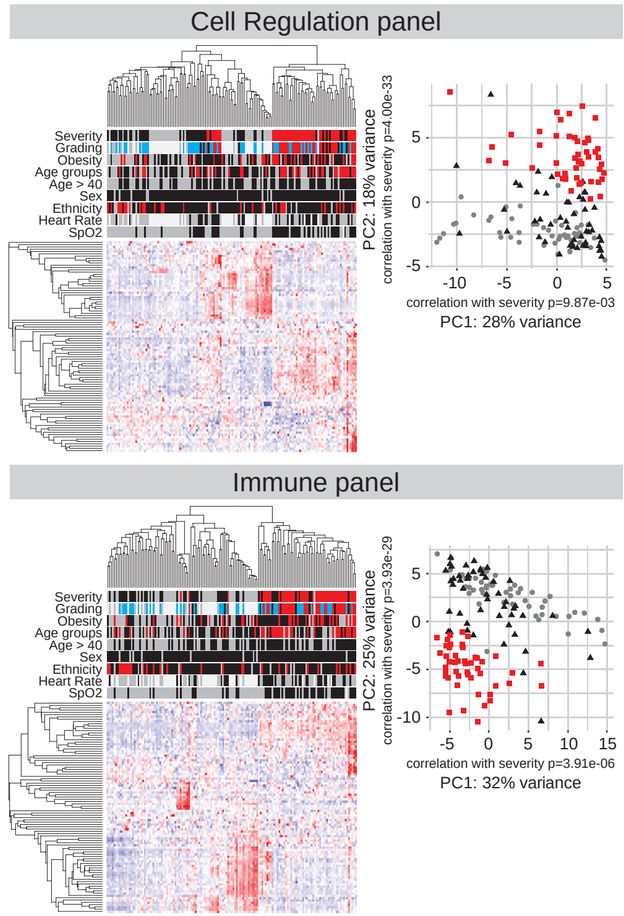
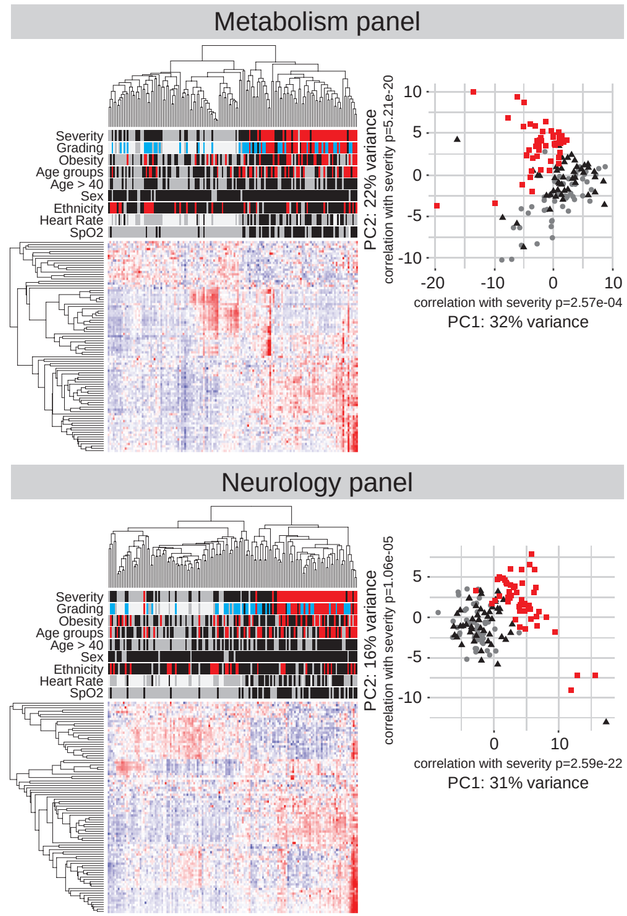
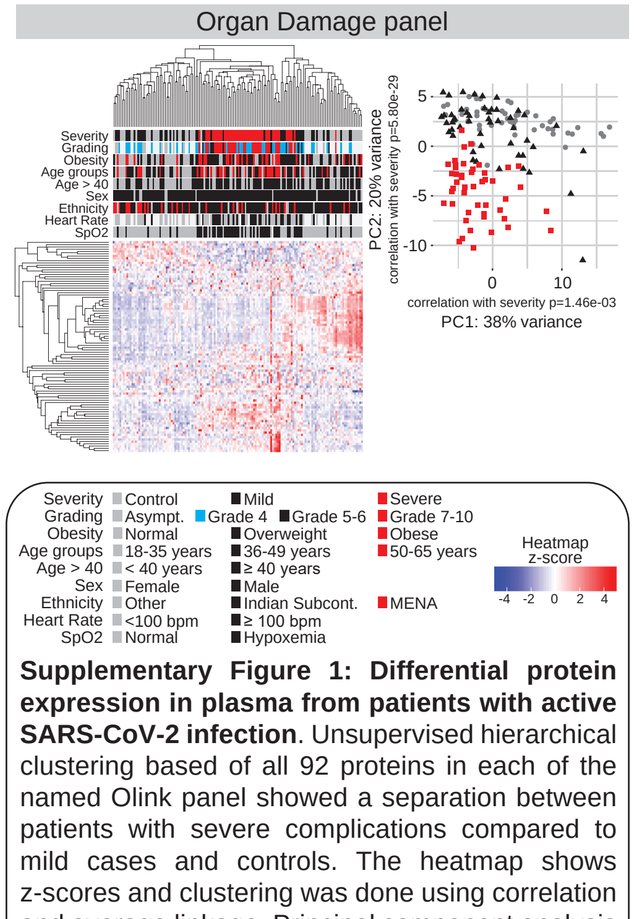
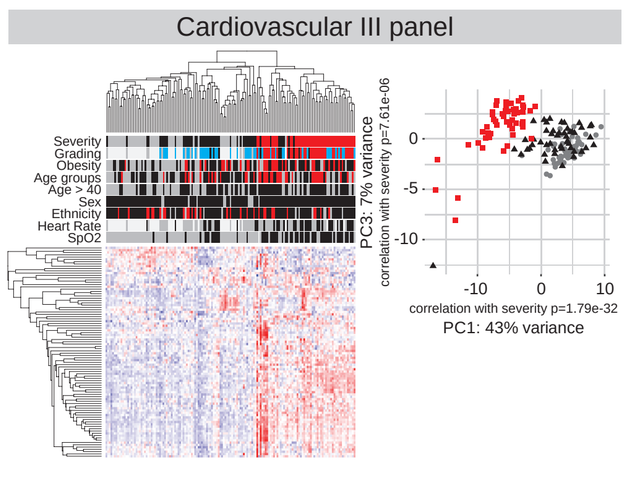
Content

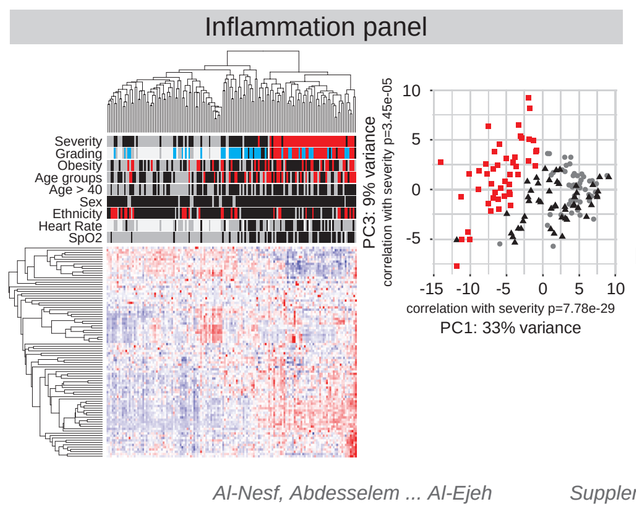


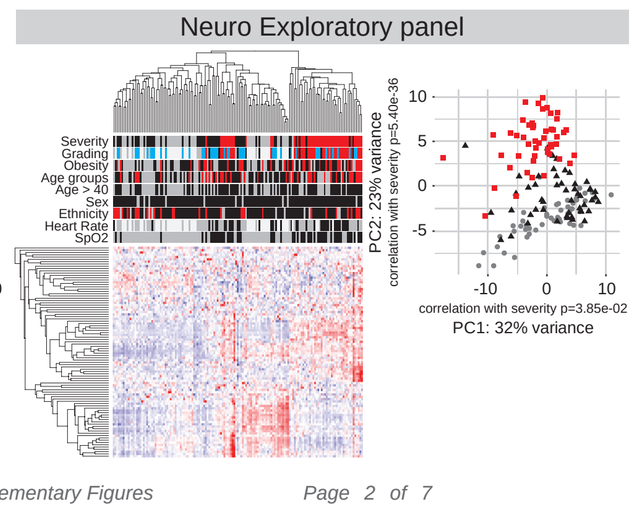




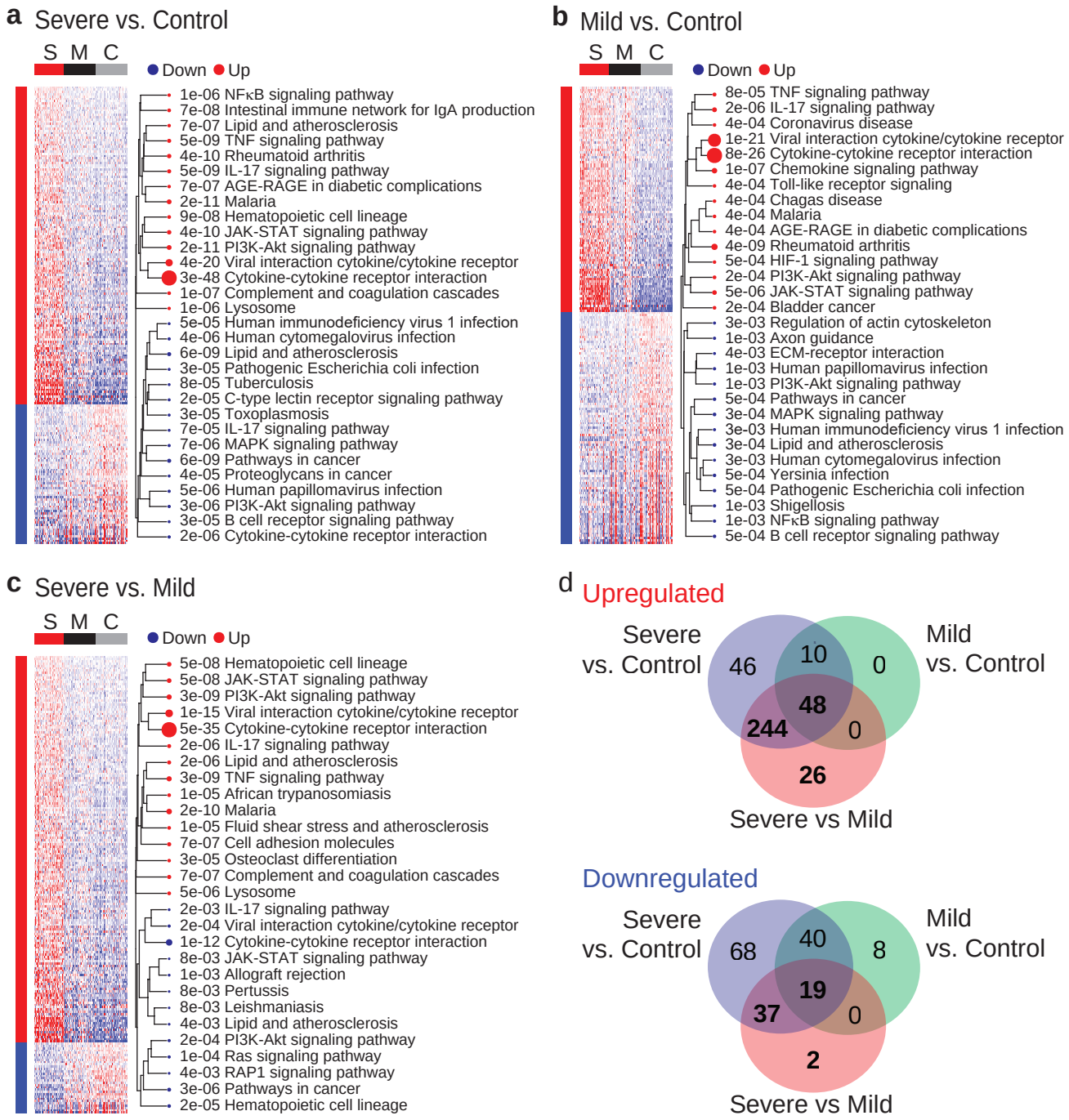




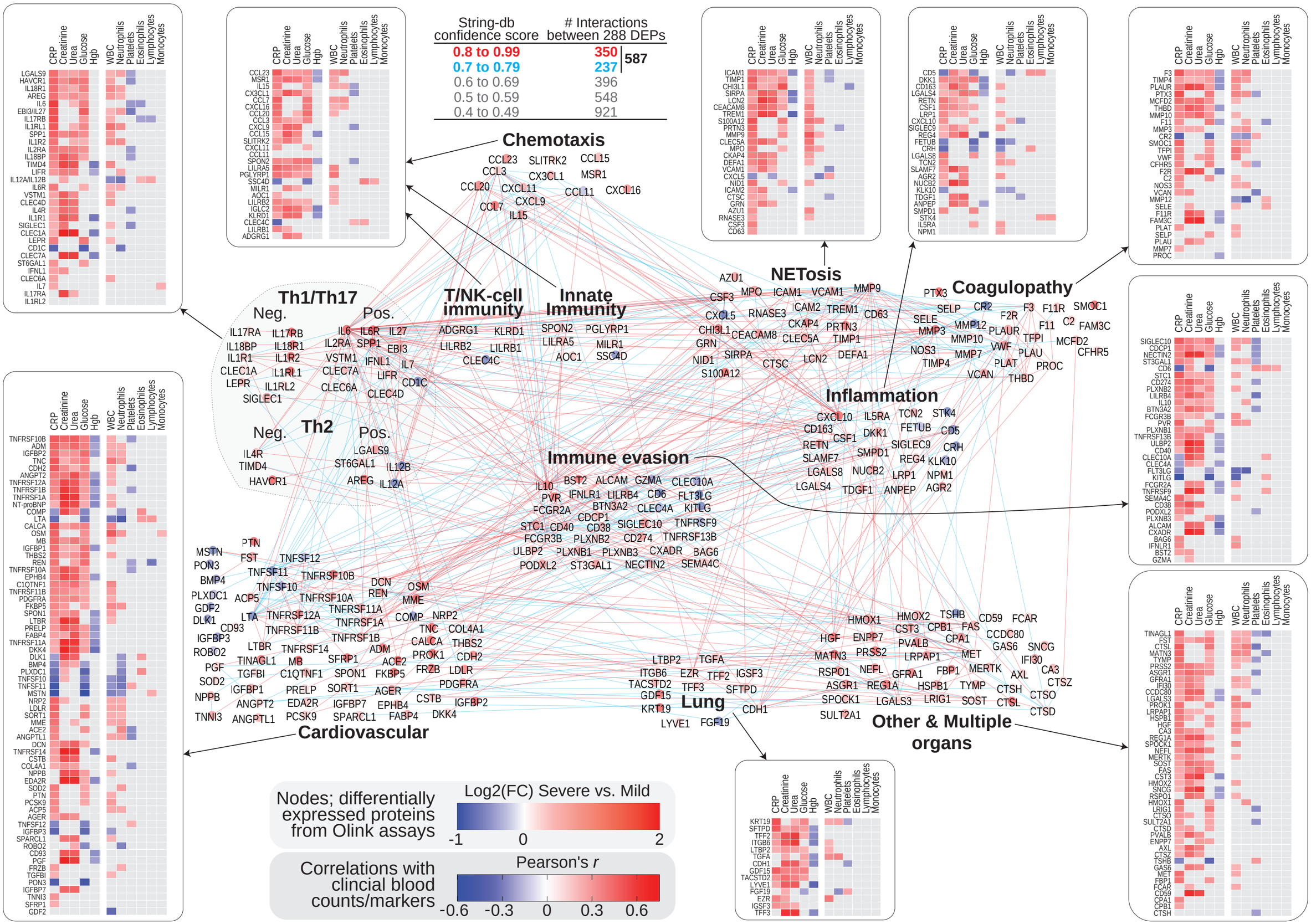




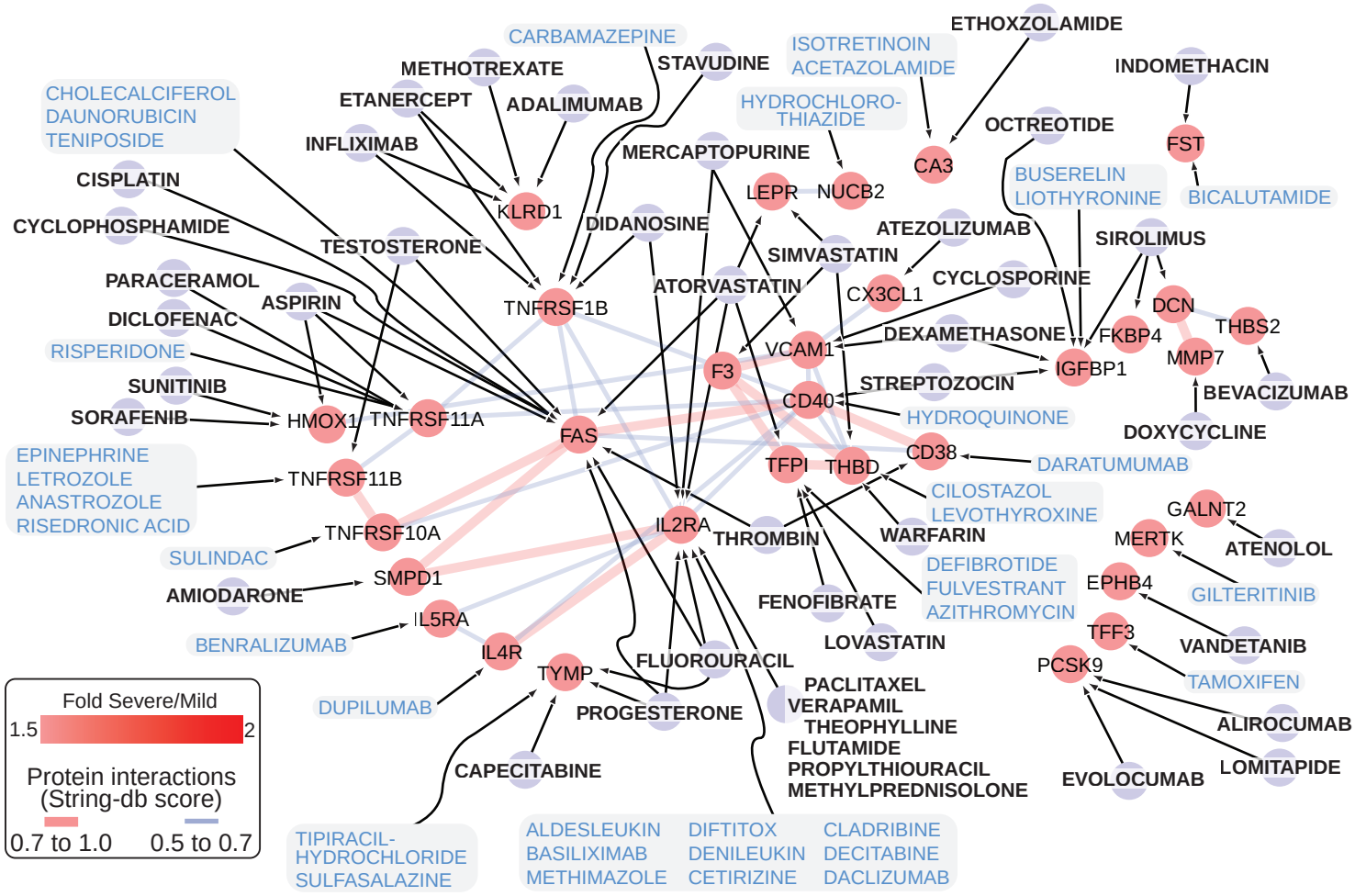
Supplementary Figure 1: Differential protein expression in plasma from patients with active SARS-CoV-2 infection. Unsupervised hierarchical clustering based of all 92 proteins in each of the named Olink panel showed a separation between patients with severe complications compared to mild cases and controls. The heatmap shows z-scores and clustering was done using correlation and average linkage. Principal component analysis (PCA) tested the separation of the severe cases based on the expression profiles of all proteins. The limma package was used to identify differentially expressed proteins (DEPs) from the single Olink panels defined as protein with more than 1.25-fold change with a p-value of <0.05 and FDR <0.1. Differential expression analysis addressed severity as the main effect and included obesity, age, sex, ethnicity, heart rate and SpO2 to correct for the interaction of these factors with disease severity. A summary of the number of DEPs for each panel is shown in Figure 1a.



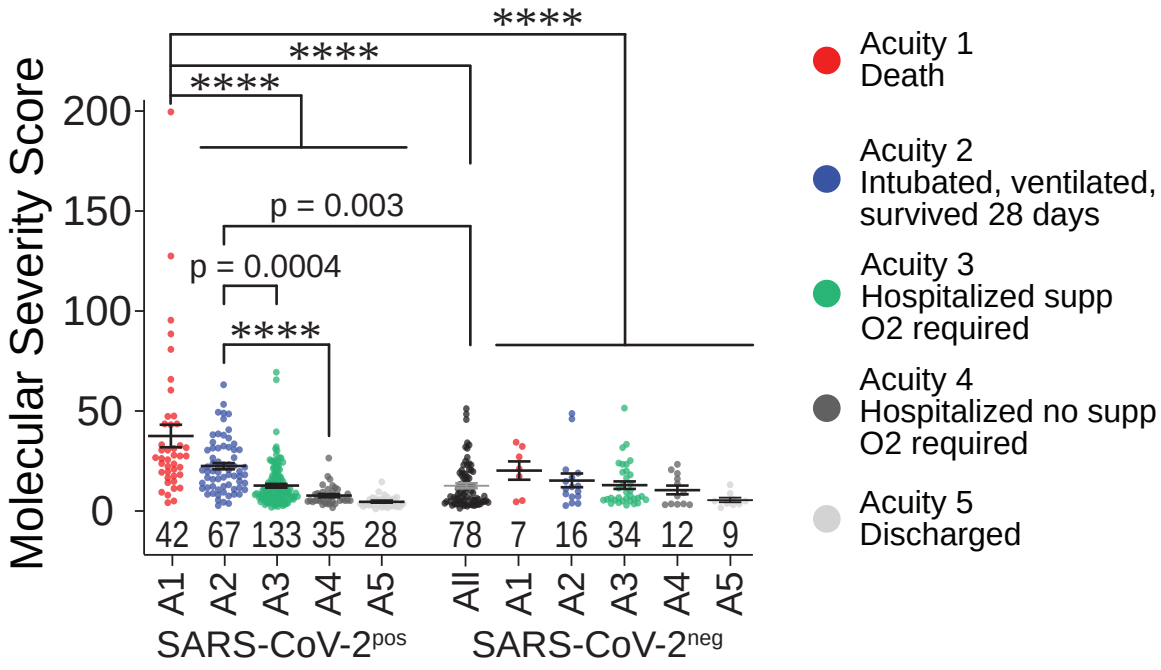
Supplementary Figure 2: Functional analysis of differentially expressed proteins in plasma of patients with active SARS-CoV-2 infection. (**a-c**) Heatmaps of the expression differentially expressed proteins (DEPs) in severe (S) and mild (M) cases and control (C) are shown to the side of enrichment trees of enriched KEGG pathways using DEP.92. Upregulated and downregulated proteins and pathways are shown in red and blue respectively. The p-value for enrichment is depicted by the size of the circles in the enrichment trees. (**d**) Venn diagrams summarizing the shared and unique upregulated (top) and downregulated (bottom) DEPs. The identities of the proteins in each Venn diagram are shown in Supplementary Data 3.



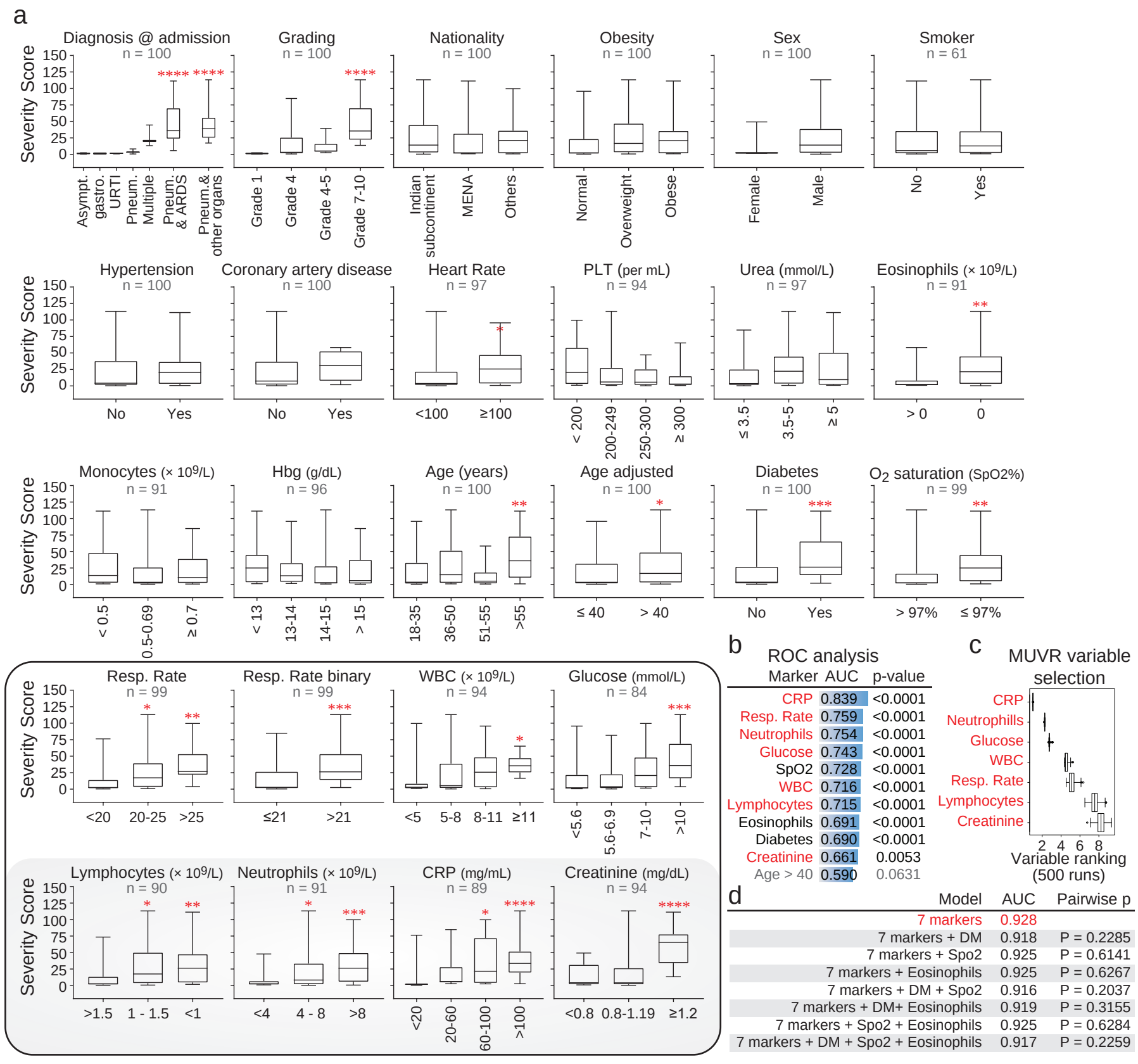
Supplementary Figure 3: Functional networks of deregulated plasma proteins in severe versus mild COVID-19 disease. Differentially expressed proteins (DEPs) in patients with severe complications compared to mild-moderate disease were subjected to network analysis using the STRING database and annotation for their function as circulating proteins (**Supplementary Data 3** and **Supplementary Notes**). Of the 375 DEPs (1.25-fold change in severe vs. mild cases), 288 (77%) DEPs could be allocated to 11 functional groups considering their potential function as circulating proteins; chemotaxis, coagulopathy/fibrinolysis, immune evasion, innate immunity, T- or NK-cell immunity, T-/Th-cells dysfunction, inflammation, neutrophils/neutrophil extracellular traps (NETosis), and organ damage (lung, cardiovascular or other and multiple organs). DEPs are classified as agonists (pos.) or antagonist (neg.) for the Th1/Th17 and Th2 immune responses. The color intensities (red: upregulated, blue: downregulated; legend) depict the log2 fold-change between severe and mild-moderate cases. Interactions between the 288 DEPs are shown only for those with STRING-db confidence score ≥ 0.7 are shown (587 high-confidence interactions). Inserted table in the Figure summarizes the number of interactions across the different STRING-db confidence scores (0.4 to 0.99). The heatmaps summarize the Pearson's correlation coefficient (r) for significant correlations ($p<0.05$, two-tailed, GraphPad Prism) between each protein in the functional networks and the clinical blood biochemical markers and blood cell counts available in our cohort. Refer to **Supplementary Data 3** for the correlation r values of all DEPs with the clinical markers.



Supplementary Figure 4: Protein-drug interaction network of 1.5- to 2-fold upregulated plasma proteins in severe COVID-19. Proteins with 1.5- to 2-fold upregulation in patients with severe complications versus mild-moderate disease were subjected to protein-drug interaction (PDI) using the Drug-Gene Interaction database (DGIdb, v4.2.0). Target proteins are colored red, and the intensity depicts the fold-change. Drugs which target single proteins are shown in grey boxes and blue font and those that target multiple proteins (on this Figure or in Figure 4) are depicted in black font in blue nodes. Protein-protein interactions are colored according to the STRING-db confidence scores; red: confidence score ≥ 0.7, blue: confidence score ≥ 0.5 and < 0.7. Drugs in red bold font are notable examples discussed in the main text.



Supplementary Figure 5: The COVID-19 molecular severity score on day 0 in the SARS-CoV-2 positive and negative patients in Massachusetts General Hospital (MGH) cohort. The MGH cohort collected plasma samples on day 0 (within 24 hours of admission to the emergency department) from symptomatic patients, of whom 78 patients were found to be negative for SARS-CoV-2. The molecular severity score on day 0 was compared across the different severity levels (acuity max over 28-day period) and between SARS-CoV-2^{pos} and SARS-CoV-2^{neg} patients. Scatter plots show the calculated scores (mean ± SEM) and the number of patients in each group is stated under each plot. Only significant differences are depicted (two-way ANOVA with Tukey's multiple testing correction, GraphPad Prism); **** p<0.0001, exact p-values are stated otherwise.



Supplementary Figure 6: Comparison of the COVID-19 molecular severity score across the groups within the clinical parameters included in the study cohort. (**a**) Boxplots (median as center line, box marks 25th and 75th percentiles, and whiskers define minimum and maximum) for the score from the 12-protein signature across the stated groups in each of the clinical annotations in infected patients (n = 100). One-way ANOVA with Dunnett's multiple testing correction was used for clinical parameters with more than two groups, and unpaired two- tailed t-test was used for parameters with two groups. Significant differences are depicted as * p<0.05, ** p<0.01, *** p<0.001 and **** p<0.0001. Refer to **Supplementary Data 6** for more details of the statistical comparisons and exact p-value. (**b**) ROC curve analysis of the parameters which showed significant association with the 12-protein molecular severity score. The DeLong et al. method was used for statistical analysis. (**c**) MUVR was used for variable selection using the same parameters in panel b. Seven parameters (markers) were selected by MUVR and the boxplot summarizes the median ranking (center line), 25th and 75th percentiles (box boundaries), and minimum and maximum (whiskers) from 500 independent MUVR runs. (**d**) The model of 7 markers from MUVR was further confirmed for performance using ROC curve analysis in comparison to models which included the remaining clinical markers. There was no additional benefit from addition diabetes, SpO2 and/or eosinophil counts as judged by pairwise comparisons (DeLong et al. method) against the model of the 7 markers alone. Abbreviations; Resp. Rate: Respiratory rate, WBC: white blood cells, CRP: C-reactive protein.

Supplementary Note 1

Functional annotation and literature for Figure 2 and Supplementary Data 3. The differentially expressed proteins in patients with severe COVID-19 versus patients with mild-moderate disease were subjected to functional annotation based on information from databases and literature and concerning their role in circulation and pathogenesis.

Protein	Annotation
IL6	In addition to a strong pro-inflammatory role, IL-6 can modulate the Th1/Th2 balance towards Th2, and with TGFβ it promotes Th17 cells [1]
IL6R	sIL-6R renders cells lacking the IL-6R, but expressing gp130, responsive to IL-6 [1]; the trans-signaling is highly inflammatory [2] and maintains local Th17 cells [3]
EBI3/IL27	Both form the IL27 which potentiate the early phase of Th1 response and suppress Th2 and Th17 differentiation [4]. IL27 is a potent immunosuppressant and increased in sepsis [5]
IL12A/IL12B	Growth factor and enhance lytic activity of activated T- and NK-cells and stimulate the production of IFNG by resting PBMC. Expressed by activated macrophages. Th1 cells development [6]. Th2 cells inhibit antigen-dependent IL-12 secretion by DCs [7]
TIMD4	Ligand for HAVCR1/TIM-1, expressed on APCs such as dendritic cells or macrophages. Also called TIM-4; Soluble form may be inhibitory of cellular function TIM-4 in Th2 development [8]
HAVCR1	Also called TIM-1, receptor for TIMD4. May be a receptor for SARS-CoV-2 in lung and kidney [9]. Soluble form may be inhibitory of cellular function TIM-1 [8] including its role in regulating Th2 responses [10]. Plasma TIM-1/KIM-1 associates with stroke [11] and lower kidney function [12]. Also elevated in cardiovascular disease, worsened diastolic function [13]
LIFR	Soluble form (sLIFR) inhibits LIF function [14] and binds to OSM. sLIFR may inhibit LIF-mediated promotion of Treg lineage and repressing Th17 lineage-specific genes [15]
IL17RB	Binds to IL17B and IL17E. Soluble form is a decoy receptor produced by Th2-skewed antigen-presenting cells (APC2) [16]
IL17RA	Receptor for IL17A and IL17F. Receptor for SARS coronavirus-2/SARS-CoV-2 virus protein ORF8 [17] and sIL17RA [18] acts a decoy receptor [17]
CCL20	Chemotaxis of DCs, effector/memory T-cells and B-cells, slightly, neutrophils, but not monocytes. Recruitment of proinflammatory IL17 producing Th17 and Treg cells to sites of inflammation [19]
VSTM1	VSTM1-v2 (soluble isoform) behaves as a cytokine, promoting IL17A secretion by CD4+ T-cells, and differentiation and activation of IL17 producing Th17 cells [20]
IL1R1	Mechanism for neutralization of IL1B by secreted/soluble receptors [21], which interferes with the critical role of IL-1 in Th17 differentiation [22, 23]
IL1R2	Secreted IL1R2 form is dominant mechanism for neutralization of IL1B by secreted/soluble receptors [21], as a decoy receptor it interferes with the critical role of IL-1 in Th17 differentiation [22, 23], thus implicated in several pathologies including sepsis [24]

IL1RL1	Receptor for IL33. Soluble form (sST2) inhibits IL33 binding and its cardioprotective effect [25] and is elevated in patients who do not survive from sepsis [26]. IL33 is an inducer of Th2 cells [27] which is inhibited by sST2.
IL1RL2	Receptor for IL36. IL36 signaling promotes Th1 polarization [28] but soluble receptor inhibits IL36 signaling [29]
AREG	Epithelial-derived AREG (Amphiregulin) can act to promote tissue repair and integrity. AREG is also secreted by innate lymphoid cells 2 (ILC2) and other innate immune cells and might be a critical component of type 2-mediated resistance and tolerance [30]. Pathogenic memory Th2 cells induce AREG via IL-33, which reprograms eosinophils that via Osteopontin/SPP1 facilitate an inflammatory state and airway fibrosis [31]
IL18BP	Inhibitor of IL18-mediated early Th1 cytokine response, IFNG production, resulting in reduced T-helper type 1 immune responses [32]
IL18R1	IL18 receptor involved in IL18-mediated IFNG synthesis from Th1 cells [33]. Soluble form inhibits IL18-mediated IFNG synthesis from Th1 cells [34, 35]
SPP1	Upregulate INFG and IL12, essential in the pathway that leads to type I immunity and Th1-cytokine functions [36]. Also involved in pathogenic memory Th2 cells induce AREG via IL-33, which reprograms eosinophils that via Osteopontin/SPP1 facilitate an inflammatory state and airway fibrosis [31]. SSP1 is elevated in several cardiovascular pathologies [37]
IL10	Dramatic early proinflammatory IL-10 elevation may play a pathological role in COVID-19 severity proinflammation and T-cell exhaustion [38]
PVR	Also called CD155 expressed in peripheral tissue (e.g., endothelial, epithelial cells and APCs) and is the ligand for CD226 (DNAM-1) expressed on NK cells, and a subset of T-cells (stimulatory) and to TIGIT on NK-/T-cells (inhibitory) [39]. sCD155 inhibits NK-Cells CD226 mediated cytokine production, including that of IL2, IL5, IL10, IL13, and IFNG cytotoxicity [40]
ADGRG1	Receptor involved in cell adhesion and probably in cell-cell interactions. ADGRG1 (GPR56) inhibits NK-cell cytotoxicity and is cleaved/shed (sGPR56) upon activated [41]
LGALS9	By interacting with TIM3, it inhibits Th 1 and Th17 cells, but not on Th2 cells, skewing to Th2 imbalance and Tregs [42, 43]. Binding to CD40 inhibits the proliferation and survival of CD4loCD40+ effector T-cells [44]
BST2	Tetherin is induced by INFa [45, 46] and restricts cell-free virions spread by blocking the release of envelop virus including SARS-CoV1. Plasma BST2 has been described in colorectal and breast cancers [47, 48]. SARS-CoV-2 Orf7a impedes Tetherin, and both are secreted in virus like particles as an evasion mechanism [49]
SIGLEC10	Immunoregulatory role, inhibiting pathogen-related and damage-associated molecular patterns (DAMPs)-mediated inflammation [50]. Siglec-10 Sv2, a secreted form, is the most abundantly expressed transcript in PBMC and retains functionality [51]; thus, might be an evasion mechanism allowing viral spread and excessive inflammation
STC1	Despite its anti-inflammatory role, it is a phagocytosis checkpoint driving immune evasion by binding to calreticulin; thus, abrogating membrane calreticulin-directed phagocytosis by APCs (macrophages and DCs) impairing APC capacity of antigen presentation and T cell activation [52]
ST3GAL1	ST3Gal-1 in circulation is principally carried by platelets and released upon activation [53]. ST3GAL1-mediated O-linked sialylation of CD55 act as CD55-mediated immune evasion [54]

LILRB4	Binds to MHC I molecules on APCs and NK-/T-cells and inhibits immune and inflammatory responses to regulate autoimmunity [55]. Soluble form is produced by splice variant [56]. Soluble form (sLILRB4) suppresses T cell responses and elicits T-cell anergy or activation of Treg or T suppressor cells [56-58]
NECTIN2	Also called PVRL2, expressed in peripheral tissue (e.g., endothelial, epithelial cells and APCs) and is the ligand for CD226 (DNAM-1) expressed on NK cells, and a subset of T-cells (stimulatory) and to PVRIG on NK-/T-cells (inhibitory) [39]. sNECTIN2 [59, 60]. Soluble form is inhibitory
SIGLEC1	Macrophage-restricted expressed resident and inflammatory macrophage mediating cell interactions to granulocytes, monocytes, NK-cells, B-cells and CD8 T-cells [61]. Soluble form (sSIGLEC1) associates with the INF type-I transcriptional signature and a biomarker of renal disease in SLE [62]. The soluble form is encoded by a variant transcript and is functional [63] which can be suppressive of function: reduce numbers of infiltrating Th1 and Th17 cell, higher numbers of Treg cells [64]
PODXL2	Cell surface transmembrane proteins ligand for vascular selectins mediates rapid rolling of leukocytes over vascular surfaces [65]. Cleaved [66, 67]; the soluble form is inhibitory [67] and would inhibit leukocytes recruitment site of injury during inflammation
CD274	PD-L1 modulates the activation threshold of T-cells and limits T-cell effector response. sPDL1 induced immune suppression and damage, and associates with COVID-19 pathogenesis and mortality [68]
IFNL1	INF lambda 1 (type-III INF, also called IL29) involved in antiviral host defense, predominantly released by epithelial tissues, including lung. Ligand for IL10RB and IFNLR1 leading to expression of IFN-stimulated genes (ISG). Significantly up-regulate IL6, IL8 and IL10 from monocytes [69] and inhibits Th2 polarization towards Th1 [70-72]
IFNLR1	IFNLR1/IL10RB dimer is a receptor for type III INFs mediating their antiviral activity. Expressed on epithelial cells within the lung, intestine, and liver [70, 72]. Soluble variant of IFNLR1 (sIFNLR1/sIFN-λR1), inhibits antiviral and immune effect of type III INF signaling/ISG induction [73]
PGLYRP1	Pattern recognition receptor in innate immunity, promotes the activation of monocytes/macrophages and enhances the inflammatory response [74]. Able to kill virus-infected cells [75]. High in cardiovascular disease and heart failure [76, 77]. It also binds to TNFRSF1A/TNFR1 and inhibit of TNFα cytotoxic activity [78]
CD38	Enzyme and moonlights as a receptor on immune cells (B-, T-, NK-Cells), upregulated by inflammatory mediators, and used as a cell activation marker [79]. Released to blood as a soluble form which inhibits binding to the membrane form, inhibiting adhesion to endothelial cells and immune cell chemotaxis [80] but retains its enzymatic function [81]
IL2RA	IL2 receptor regulates immune tolerance by controlling Tregs. Soluble form enhances the development of Th17 responses [82] and increased in association with cardiovascular events [83]. Soluble IL2RA (sCD25) is elevated in severe COVID-19 [84]
LEPR	Soluble LEPR inhibits Leptin's effects on enhancing the immune response via activating APCs, Th1/Th17 cells function and proliferation, and suppresses Th2 cytokine production [85, 86]

CDCP1	Cell adhesion and cell matrix association; ligand for CD6. Shedding and a soluble isoform leads to sCDCP1, occurs during tissue injury [87, 88]. sCDCP1 can bind CD6 [89], reduces Th1 and/or Th17 immune responses or acts as T-cell chemoattractant [90]. High sCDCP1 and sALCAM along with reduced sCD6 suggest reduced T-cell activation
ALCAM	Promotes T-cell activation and proliferation via interaction with CD6 but the soluble form (sALCAM) abolishes this function. High sCDCP1 and sALCAM along with reduced sCD6 suggest reduced T-cell activation. Shed by platelets [91]
CD6	Interaction with ALCAM/CD166 functions as costimulatory molecule; promotes T-cell activation and proliferation. Soluble CD6 (sCD6) - shedding - indicates activation of T-Cells but leads to inhibition of T-cells [92]. High sCDCP1 and sALCAM along with reduced sCD6 suggest reduced T-cell activation
PLXNB1	Plexin-Semaphorin. Expressed by activated T cells, immature bone marrow-derived DCs, and lung DCs [93] and platelets [94]. Plexin B1-B3 members have a convertase cleavage site [95]. sPLXNB1 (isoform or cleaved) may neutralize SEMA4D functions [96] which include T-cell priming, B-cell survival and antibody production in response to T-dependent antigens, monocyte paralysis and the arrest of its spontaneous and chemokine-induced migration [97]
PLXNB2	Plexin-Semaphorin. Expressed on macrophages, DCs and plasmacytoid DCs [95]. Receptor for SEMA4C. Negatively regulates macrophage migration. Optimal activation and differentiation of CD8+ T Cells [98]. Plexin B1-B3 members have a convertase cleavage site [95]. Cleavage releases sPLXNB2 [66] would interfere with CD8+ T-cell activation
PLXNB3	Plexin-Semaphorin. Disruption of focal adhesions and cellular collapse as well as inhibition of cell migration and invasion. Plexin B1-B3 members have a convertase cleavage site [95]. Shed by platelets [91]; soluble form would block SEMA5A effect of increased T- and NK-cell proliferation and induced the secretion of proinflammatory Th1/Th17 cytokines [99]
SEMA4C	Plexin-Semaphorin. Ligand for PLXNB2, required for Tfh cells to migrate to the GC and a marker of memory B-cells and B-cells stimulated by Th2 cytokines [100, 101]. Both soluble PLXNB2 and SEMA4C marks the block of their function
RNASE3	Released during degranulation/activated eosinophils [102, 103], and released in neutrophil NETs [104]. Cytotoxin activity [105] and may play a role in neutrophil transendothelial migration
ULBP2	Ligand for the NKG2D killer activation receptor on NK-cells mediating cytotoxicity and release multiple cytokines/chemokines. Soluble/secreted ULBP2 inhibits NK-cells as a mechanism to evade immunosurveillance by NK cells [106, 107]
IL4R	IL4 response is involved in promoting Th2 differentiation but the soluble form can inhibit IL4-mediated cell proliferation and IL5 upregulation by T-cells [108]
IL7	Forms a heterodimer with HGF. Important for proliferation during certain stages of B-cell maturation, T and NK cell survival [109]. Induces Th1 and Th17-associated cytokine secretion [110]. Elevated serum IL7 levels associates with COVID-19 [111]
BTN3A2	Plays a role in T-cell responses. Inhibits the release of IFNG from activated T-cells. sBTN3A may prevent T-cells from exerting their cytotoxic activity [112, 113]
CXADR	Role in tight junction integrity, transepithelial migration of leukocytes and neutrophils (interaction with JAML) [114, 115] and with JAML co-stimulation of epithelial γδ T cell activation [116]. Soluble form (sCAR) inhibits viral entry and inhibit other functions

SPON2	Innate immune response and a unique pattern-recognition molecule in the ECM [117]
KLRD1	Inhibitory receptor on NK-cells and memory/effector CD8-positive T cells. sKLRD1 has been reported in HIV patients [118]. May be reversing NK-cell suppression
AOC1	Digestive enzyme degrades compounds involved in allergic and immune responses, cell proliferation, tissue differentiation, tumor formation, and possibly apoptosis. Eosinophil and granulocytes increase diamine oxidase activity and release in acute inflammation [119-122]
ST6GAL1	Attachment of sialic acids to glycoproteins as a posttranslational modification influences cellular responses. Produced by platelets [123] and other cells and known as an acute phase reactant where blood level is upregulated during systemic inflammation [124]. Prolongs the activity of TNF, NFκB and STAT3 promoting the inflammatory phenotype of monocytic cells [125]. Enhances B cell IgG production and increases blood IgG titers [126]. Th2 polarization and M2 macrophages [124]
BAG6	BAG6 on exosomes a ligand of NK-cells receptor NCR3 and stimulates NK cells cytotoxicity but soluble ligand BAG6 suppressed NK-cells [127-129]
LILRB1	Binds to MHC I molecules on APCs and NK-/T-cells and inhibits immune and inflammatory responses. Soluble form is produced by splice variant and reverses the inhibition of NK cell cytotoxicity [56]
LILRB2	Binds to MHC I molecules on APCs and NK-/T-cells and inhibits immune and inflammatory responses. Soluble form is produced by a splice variant [56]. Soluble form (sLILRB2) blocks this immunosuppressive function and activates T-cells [130]
MILR1	Inhibitory role in the degranulation of mast cells. Also expressed on DCs, macrophages and neutrophils [131] - myeloid immunity. Serum MILR1 level associates with increased mast cells in circulation [132], may reverse the inhibitory role of membrane MILR1
SIGLEC9	Expressed on monocytes, neutrophils, B cells, NK cells, and minor subsets of T cells such as NK-cells as a vital inhibitory group. Engaging SIGLEC9 signaling suppresses neutrophil-mediated immunity, including inhibiting NETosis [133]. sSIGLEC9 inhibits its suppressive effect on neutrophils [134]. Soluble Siglec9 (sSIGLEC9) in the plasma can induce oxidative stress, and its expression can be increased by TNF-α, IL-6, and IL-8 [135]
LILRA5	Expressed on neutrophils, triggering innate immune responses, production of inflammatory signals such as IL6 and stimulate the early phases of immune responses [136, 137]
GZMA	T- and NK-cells specific serine protease for lysis of target cells. Reduced levels in COVID-19 severe patients associate with impaired NK- and cytotoxic T cell functions [138, 139]
CD1C	Antigen-presenting protein on DCs [140] presents to T-cell receptors on NKT-cells [141]. Soluble form would inhibit CD1C role in promoting Th1/Th17 function [140]
KITLG	Also called SCF. KITLG/SCF binding can activate several signaling pathways. Soluble form [142] secreted by fibroblasts and endothelial cells attracting mast cells.
FLT3LG	Stimulates the proliferation and differentiation of various blood cell progenitors [143]. sFLT3LG expands immature B-cells, NK-cells and DCs
SSC4D	Regulation of both innate and adaptive immune responses. Scavenger receptor [144]
IGLC2	Immunoglobulin Lambda Constant 2 (IGL@). Upregulated in plasma of critical (ICU) COVID-19 patients vs severe/mild [145, 146]

CKAP4	Anchoring of the endoplasmic reticulum to microtubules. Neutrophil degranulation [147]
GRN	Regulator of lysosomal function and as a growth factor involved in inflammation. Neutrophils produce progranulin and elastase capable of cleaving progranulin into granulin peptides promoting inflammation. High in cardiovascular disease [76]
CXCL5	Secreted by eosinophils and neutrophils [148] in response to inflammatory cytokines IL-1 or TNFα. Neutrophil activation [148, 149]
IL15	Stimulates phagocytosis of neutrophils [150, 151] and promotes T-cell proliferation during inflammation [152]
VCAM1	Expression by cytokine-activated endothelium. Neutrophil elastase and cathepsin G released by neutrophils cleaves VCAM1. Soluble VCAM1 (sVCAM1) is elevated in endothelial dysfunction and inflammation/fibrosis [153, 154]. Shed by platelets [91]
CD63	Receptor for TIMP1, leukocytes adhesion onto endothelial cells and a known marker for exosomes. Neutrophils/platelets degranulation [155, 156]
MMP9	Involved in local proteolysis of the ECM and in leukocyte migration. Roles in neutrophil-derived vascular endothelial damage and wound healing [157]. Associates with cardiovascular and respiratory failure in COVID-19 [158]
MSR1	Macrophage scavenger receptor glycoproteins (also called SR-A) implicated in the pathologic deposition of cholesterol in arterial walls during atherogenesis. Soluble form is high in arthritis inflammatory progression concomitant with increased Th17 response [159]. Neutrophil SRA expression is increased in sepsis and facilitates NETosis [160]
TREM1	Receptor involved in amplifying inflammatory responses. Soluble TREM1 is elevated during infection and shown to be a marker of sepsis and mortality [161]. Neutrophil stimulation/degranulation releases soluble TREM1 which can inhibit TREM1 receptor–mediated proinflammatory cytokine production [162]
AZU1	Expressed in specialized lysosomes of the neutrophils. Mediating recruitment of monocytes in the second wave of inflammation. Released in neutrophil NETs [104]
CEACAM8	Activated neutrophils, neutrophil degranulation. Released in neutrophil NETs [104], associates with acute-phase response, inflammation and immune response [163]
MPO	Major component of neutrophil azurophilic granules and mediates activation. Elevated in Severe COVID-19 [84]. Also cleaved from vascular endothelium by proteases [164]
PRTN3	Serine protease degrades ECM. Released in neutrophil NETs [104]
S100A12	Also called EN-RAGE and plays a prominent role in the regulation of inflammatory processes and immune response. Implicated in COVID-19 severity [165]
SIRPA	Released in neutrophil NETs [104]. SIRPα on macrophages interaction with CD47 on RBCs prevents phagocytosis [166]; soluble form might block the phagocytosis inhibition
CTSC	Cathepsin C. Activation of various pro-inflammatory serine proteases from neutrophils and mast cells [167]. Neutrophilic lung inflammation [168]
CHI3L1	Th2 inflammatory response and IL13-induced inflammation, DCs accumulation and M2 macrophage differentiation [169, 170]. Released by neutrophils [170-172]

CSF3	G-CSF induces granulocytes and neutrophils release [173]
DEFA1	A definsin abundant in the granules of neutrophils and other cells [174]. Elevated in plasma during infection and inflammation [174, 175]
LCN2	Innate immunity [176] and elevated in severe COVID-19 [177]
NID1	Basement membrane glycoprotein, role in cell interactions with ECM. Promotes neutrophil adhesion and has a potent chemotactic activity for neutrophils [178]. Cleaved from vascular endothelium by proteases [164].
TIMP1	Metalloproteinase inhibitor. Growth factor/integrin signaling via CD63 and ITGB1. Neutrophilia via CD63 [179]. High in cardiovascular disease [180]. Cleaved from vascular endothelium by proteases [164]
F3	Tissue factor (TF) function in blood (extrinsic) coagulation initiation forming a complex with circulating factor VII or VIIa. Blood TF contributes to thrombosis [181] and associates with sepsis [182] and acute myocardial infarction [183, 184]
PROC	Protein C regulates blood coagulation by inactivating factors Va and VIIIa and cellular anti-inflammatory signaling (THBD/EPCR/PAR-1[cleaved by PROC instead of thrombin]) [185]. Circulating form is pro-enzyme/zymogen (not activated)
NOS3	eNOS plays crucial roles in regulating vascular tone, leukocyte adhesion, platelet aggregation, and anti-inflammatory role. eNOS was reported in plasma and serum [186, 187]; endothelial cell death may release eNOS during sepsis and oxidative stress, suggesting eNOS uncoupling with proinflammatory and coagulopathy consequences [188, 189]
PLAT	tPA generates plasmin, involves in tissue remodeling and degradation. High serum levels in acute myocardial infarction [190, 191]
TFPI	Antithrombotic against factor x from the extrinsic coagulation pathway. Increased in critically ill COVID-19 patients [192]
MCFD2	Plays a role in the secretion of coagulation factors (factors V and VIII) [193]. MCFD2 is secreted via a classical secretion pathway [194]
MMP10	Thrombin induces endothelial MMP10 levels through a PAR1 (F2R)-dependent mechanism. MMP10 serum levels associate with inflammatory markers and arterial diseases [195-197]
MMP3	Activated by plasmin and activates MMP7. MMP3 serum levels are associated with inflammatory markers and COVID-19 severity [198]
FAM3C	Promotes EMT, relevant to inflammation/fibrosis. Released by platelets [199]
MMP7	Activated by plasmin. Serum level associate with lung fibrosis, COVID-19 severity, and other diseases [177, 200, 201]
CR2	Also called CD21 is receptor for complement C3 and binds to CD19 on B-cells. Soluble CD21 in the blood is mainly derived from follicular DCs [202] and it competes for C3 binding and inhibits CD21-CD19 B-cell activating function [203]
F2R	Also called PAR1, a receptor for activated thrombin expressed in platelets and endothelial cells mediating the interplay between coagulation and inflammation [204]. Shedding makes PAR1 unresponsive to thrombin [205]

PLAU	Converts plasminogen to plasmin and leads to D-dimers [206], function as stimuli for inflammatory cell (neutrophils, monocytes, macrophages) production of cytokines. TNFα or IL-1 induce the expression of uPA from endothelial cells [207, 208]
THBD	Thrombomodulin is a cofactor in the thrombin-induced activation of protein C (PROC). Soluble thrombomodulin associates with mortality, hospital stay and ICU in COVID-19 patients [209]. Cleaved to its soluble form by neutrophil elastase during acute and chronic inflammatory responses immunologic reactions and complement activation [210]
C2	Part of the classical pathway of the complement
CFHR5	The dimerized forms have avidity for tissue-bound complement fragments and efficiently compete with the physiological complement inhibitor CFH [211]
F11	Blood (intrinsic) coagulation by activating factor IX
MMP12	Degrades soluble and insoluble elastin. Role in countering neutrophil infiltration, clearing NETs, and dampening inflammatory pathways [212]
PLAUR	High level of suPAR associates with COVID-19 severity [213], suPAR levels are positively correlated with high-sensitivity C-reaction protein (hs-CRP), neutrophil/leukocyte ratio, and lymphocyte counts [214]. Cardiovascular disease [13]
TIMP4	Protease inhibitor, inhibits platelet aggregation and recruitment [215]
VWF	Promotes adhesion of platelets to the sites of vascular injury [216]
PTX3	Acute phase response protein, activates the classical pathway of complement activation and facilitates pathogen recognition by macrophages and DCs [217-220]
VCAN	Involved in inflammation-related interactions with leukocytes and chemokines to recruiting inflammatory cells, particularly in inflammatory lung conditions. Cleaved by MMPs and plasmin and presence in circulation promotes coagulation [221]. Cleaved from vascular endothelium by proteases [164]
SMOC1	Promoting endothelial cell proliferation and angiogenesis [222] and coagulation [223]
LTA	Homotrimeric form binds to TNFRSF1A/TNFRSF1B/TNFRSF14. Heterotrimeric form with LTB binds to TNFRSF3/LTBR. Lymphotoxin is produced by lymphocytes as a cytotoxic. Increased in cardiovascular disease [180]
LTBR	TNFRSF3 is receptor for LTA/LTB and TNFS14/LIGHT, promotes apoptosis and role in lymphoid system. High levels of circulating LTβR associated with cardiovascular risk factors, multiple inflammatory markers, and markers of cardiac injury [224]
TNFRSF1A	Receptor for TNFSF2/TNFa and homotrimeric TNFSF1/LTA. Contributes to the induction of non-cytocidal TNF effects including anti-viral state. Shed off neutrophils and T-cells [225-227]. Soluble sTNFR1 associates with nephropathy, cardiovascular events, heart failure [228-230]
TNFRSF1B	Receptor for TNFSF2/TNFa and homotrimeric TNFSF1/LTA, mediates most of the metabolic effects of TNFa. It is shed of neutrophils and T-cells [225-227]. Soluble form (sTNFR2) associates with nephropathy, cardiovascular events, heart failure [228-230]
TNFRSF14	Receptor for TNFSF14/LIGHT and homotrimeric LTA. Has different cis/trans signaling with activating/inhibitory effect on immunity. Soluble form (sHVEM), by cleavage, is increased during inflammation and inhibits LIGHT function. Increased in severe COVID-19 [231]

TNFSF11	RANKL binds to TNFRSF11B and TNFRSF11A. Augments the ability of dendritic cells to stimulate naive T-cell proliferation. sRANKL decreased in coronary artery disease [232, 233]
TNFRSF11B	OPG is a decoy receptor for TNFSF11/RANKL and thereby neutralizes its function [234]; it is upregulated in coronary heart disease [232]
TNFRSF11A	TNFRSF11A/RANK is a receptor for TNFSF11. Involved in the regulation of interactions between T-cells and dendritic cells [235]
CD40	Receptor for TNFSF5/CD40LG. Mediates a broad variety of immune and inflammatory responses. Soluble CD40 has immunosuppressive effects, reduced T-Cells and INFγ secretion, and is elevated in atherosclerotic vascular disease [236]
TNFSF10	TRAIL binds to TNFRSF10A/TRAIL-R1, TNFRSF11B/OPG and others. Binding to the decoy receptor OPG cannot induce apoptosis. sTRAIL correlates with inflammatory cytokines and CD68 expression and plaque cell apoptosis, plaque inflammatory activity, and with symptomatic carotid plaques [237]
TNFRSF10A	TRAIL-R1. Promotes the activation of NF-kappa-B. Essential for ER stress-induced apoptosis. Soluble TRAIL-R1 (sTRAIL-R1) has been reported in cancer [238, 239] and ankylosing spondylitis [240]
TNFRSF10B	TRAIL-R2 promotes the activation of NF-kappa-B. Essential for ER stress-induced apoptosis. Higher plasma levels of sTRAIL-R2 had a higher risk of future cardiovascular events [13]. sTRAIL-R2 correlates with inflammatory cytokines and CD68 expression and plaque cell apoptosis, plaque inflammatory activity, and with symptomatic carotid plaques [237]
TNFSF12	TWEAK. Promotes angiogenesis and the proliferation of endothelial cells [241]. Induction of inflammatory cytokines [242]. Promotes IL8 secretion [243]
TNFRSF12A	Receptor for TNFSF12/TWEAK. Promotes angiogenesis and the proliferation of endothelial cells. Soluble form (sFn14) has been described acute and chronic kidney diseases [244]
TNFRSF13B	TACI is a receptor that stimulates B- and T-cell function and the regulation of humoral immunity T-independent humoral response [245, 246]. Soluble form acts as a decoy receptor inhibiting ligand-mediated B-cell survival/function and NFκB-activation [247]
TNFRSF9	Soluble forms (sCD137) released by activated T cells [248] is antagonistic and reduces immune activity [249, 250]. High in cardiovascular disease [180, 251]
EDA2R	Mediates the activation of the NF-kappa-B and JNK pathways. Shed form reported [252] and protects from apoptosis. High in cardiovascular disease [180]
FAS	Receptor for TNFSF6/FASLG. The secreted isoforms 2 to 6 (sCD95) block apoptosis [253], elevated in liver disease [254], kidney injury [255], angina [256]
CXCL16	Scavenger receptor on macrophages, which specifically binds to OxLDL (oxidized low-density lipoprotein). A secreted splice variant by DCs is a chemoattractant for CXCR6+ cells [257]
SLITRK2	Released in neutrophil NETs [104]. Expressed predominantly in neural tissues and have neurite-modulating activity. Suppresses neurite outgrowth (Axonogenesis) and may be involved in leukocyte chemotaxis [258]
CCL11	Promotes the accumulation of eosinophils, but not mononuclear cells or neutrophils, a prominent feature of allergic inflammatory reactions [259]

CCL15	Attracts T-cells and monocytes, but not neutrophils, eosinophils, or B-cells (UniProtKB)
CCL23	Attracts monocytes, resting T-Cells, and neutrophils, not activated lymphocytes (UniProtKB)
CCL3	Attracts inflammatory cells; macrophages, monocytes and neutrophils [260]
CCL7	Attractant for monocytes and eosinophils, not neutrophils (UniProtKB)
CX3CL1	Soluble form is chemotactic for T-cells and monocytes and not for neutrophils [261]
CXCL11	Attractant for interleukin-activated T-cells but not unstimulated T-cells, neutrophils, or monocytes (UniProtKB)
CXCL9	Attractant for activated T-cells (UniProtKB)
CLEC5A	Activation of CLEC5A on neutrophils and macrophages induce neutrophil extracellular trap (NET) formation and proinflammatory cytokine release [262, 263]
CLEC4D	Expressed in resting macrophages [262]. CLEC4D modulates T-cells toward effector T-helper 1 and T-helper 17 cell subtypes [264]
CLEC7A	Expressed in DCs, neutrophils and other immune cells and engages signaling cascades that drive innate and adaptive immunity, inflammatory cytokine secretion and DC maturation to prime CTL CD8+ and Th1/Th17 cells [262]
CLEC1A	Expressed on APCs, myeloid cells, and ECs and reduces Th17 differentiation and increases Tregs [265-267]. Soluble form inhibited the HRG-induced neutrophil rounding, phagocytic activity, and prolongation of survival time [268]
CLEC6A	Expressed in macrophages, monocytes, neutrophils and several DC subtypes and activation leads to cytokines release and induce a mixed Th2/Th17 response [262]
CLEC4A	Expressed on monocytes, macrophages, granulocytes, B cells, and DCs cross-presentation to CD8+ T cells [262]
CLEC10A	Expressed in subsets of DCs and macrophages and is used as a marker of alternative macrophage activation and plays an anti-inflammatory role [262]
CLEC4C	Antigen capturing by DCs; its reduction is a marker of DCs maturation [262, 269]
CD5	Regulation of T-cells and B-cells [270]. Soluble form of CD5 associate with autoimmune disease and inflammation/sepsis patients [271], sCD5 as decoy receptor for the treatment of inflammation/sepsis [270]
CXCL10	CXCL10 is secreted by several cell types in response to IFN-γ. These cell types include monocytes, endothelial cells and fibroblasts [272] chemoattraction for monocytes, macrophages, T cells, NK cells, and DCs, promotes T cell adhesion to endothelial cells [273]
RETN	Adipokine associated in several pathologies including cardiovascular disease [274], and pro-inflammatory effect [275] with levels are correlated with inflammatory and fibrinolytic markers such as CRP, TNF-α, and IL-6 [274]
AGR2	Secreted in mucus including the lungs and modulates cell migration/adhesion, cell differentiation and cell growth. Pro-inflammatory [276]

IL5RA	Subunit of the Interleukin-5 receptor. Soluble IL5RA (sIL-5Rα) is encoded [277] and increases with the eosinophil count [278], functional impairments in B cells and eosinophils [279] and would inhibit the protective effect of IL-5 during sepsis [280]
DKK1	Antagonist of the Wnt/β-catenin signaling pathway. Increase in blood is associated with inflammation and infection [281]
TDGF1	Also called Cripto-1, exists as cell-associated and secreted (shedding by TMEM8A) form signaling in cis and trans. Cripto-1 enhances macrophage phagocytic activity and upregulates the production of pro-inflammatory cytokines [282], also enhances pro-inflammatory TNFα from CD4+ T helper cells [283]
SMPD1	Secreted form [284] is increased in response to stress and inflammatory mediators (IL1B and TNF) and viral infection [285] and coagulation during SARS-CoV-2 [286]. Converts sphingomyelin to ceramide which facilitates SARS-CoV-2 infection [287, 288]
NUCB2	Release of tumor necrosis factor from vascular endothelial cells [289]; regulate inflammatory responses [290]. NUCB2/nesfatin-1 correlated positively with plasma levels of IL6, and TNFα, IL8 in chronic obstructive pulmonary disease [291]
TCN2	Vitamin B12-binding and transport protein, high serum levels in inflammation/infection and liver disease, and characteristics of acute-phase reactant [292, 293]
NPM1	Several cellular processes. NPM1 can be passively released by necrotic or damaged cells, or secreted by endothelial cells, monocytes, and macrophages under stress/infection. Released in neutrophil NETs [104]. Extracellular NPM1 acts as a potent inflammatory stimulator promoting cytokine production. NPM described as an alarmin [294]
CSF1	M-CSF. Release of proinflammatory chemokines, role in innate immunity and inflammatory processes, influencing function of macrophages [295]
CD163	Acute phase, inflammatory response. Released from M2 macrophages during chronic inflammation/sepsis related to TNFα and TACE/ADAM17 activity [296], and cardiovascular disease [76]. A valuable diagnostic parameter for monitoring macrophage activation in inflammatory conditions including COVID-19 [297]
REG4	Involved in inflammatory and metaplastic responses of the gastrointestinal epithelium [298], polarization macrophages to M2 phenotype [299]
ANPEP	Also called CD13, expressed on small-intestinal and renal microvillar membrane. Soluble form (sCD13) is a pro-inflammatory mediator [300] and shown in severe COVID-19 [301]
CRH	Anti-inflammatory peptide released during stress and leads to cortisol production, an anti-inflammatory hormone [302]
STK4	Stress-activated, pro-apoptotic kinase. Serum STK4 levels are reduced with increased IL6 and increased inflammation [303]
LRP1	Intracellular signaling and endocytosis implicated in many biological processes. Shed by ADAM proteases. sLRP1 a biomarker of the level of atherosclerotic plaques and coronary artery events [304]. sLRP1 is generated in inflammation and may regulate inflammation by its effects on macrophage secretion of TNF-α, MCP-1/CCL2, and IL-10 [305]
LGALS8	Sensor of membrane damage caused by infection and restricts the proliferation of infecting pathogens by targeting them for autophagy. Gal-8 plays a role in innate and adaptive immunity and inflammation [306], pro-inflammatory activities in the endothelium [306]

LGALS4	Sensor of membrane damage, pro-inflammation inducing CD4+ T cells to produce IL-6 [307]
KLK10	Proteas. Represses proliferation. Inhibits endothelial Inflammation and atherosclerosis [308]
ADM	Blood pressure, hypotensive effect in blood vessels. Activates eNOS (NOS3) for NO production [309]. Strongly elevated in patients with sepsis, and in patients with hypertension and acute heart failure where high levels could reflect residual tissue congestion [310, 311]. Augments the release and production of TFPI [312] and predicts COVID-19 mortality [313]
TNC	Endothelial/inflammatory cardiomyopathy. Upregulated in blood of sepsis patients [314, 315]. Cleaved from vascular endothelium by proteases [164]
SFRP1	sFRP1 is an antagonist of Wnt signaling and is elevated in cardiovascular disease [316, 317]
CALCA	Vasodilator with high serum level associating with CAD [318, 319]
ACE2	Soluble form converts angiotensin I into the vasodilator angiotensin 1-7 [320] and associate with CVD development [321] and COVID-19 severity [322]
IGFBP2	Inhibits IGF-mediated growth. High levels associate with severity of pulmonary arterial hypertension [323]. Predictor of mortality in chronic and acute heart failure patients [324]
MME	Mature neutrophils marker, soluble form (Neprilysin or CD10) predicts heart failure [325]
NPPB	Heart failure, relates to MME inhibitors [326, 327]
FRZB	Also called sFRP3 is an antagonist of Wnt signaling and may augmenting myocardial injury-driven fibrosis [328], Cleaved from vascular endothelium by proteases [328]
NT-proBNP	Heart failure [326, 327]
OSM	Oncostatin M has a pro-inflammatory effect on cytokine production by endothelial cells, including IL-6, G-CSF and GM-CSF. Induces dedifferentiation of cardiomyocytes, promotes progression of heart failure [329]
LDLR	sLDLR reduces uptake of triglycerides and contributes to atherosclerosis [330]
CDH2	Cell adhesion protein and the soluble form inhibits cell-cell adhesion, inhibits vascular smooth muscle cell (VSMC) and macrophage apoptosis which contributes to myocardial infarction [331-333]. Released in neutrophil NETs [104]
PDGFRA	Plays a role in platelet activation, secretion of agonists from platelet granules, and in thrombin-induced platelet aggregation. Soluble form has been described [334] and might inhibit the function of membrane form leading to anti-proliferative effect on vascular endothelial cells
REN	Generates angiotensin I from angiotensinogen in the plasma, vasoconstriction, and increase in blood pressure [335]
AGER	Mediator of acute and chronic vascular inflammation. sAGER (sRAGE) is unclear for role in CVD [336]
ACP5	Serum ACP5 (TRAP/TRAP5b) higher in coronary artery disease patients and loss of bone mineral density. High in cardiovascular disease [337]
TNNI3	Cardiac Troponin I (cTnI) is exclusively expressed in adult cardiac muscle. High blood level is an indicator for myocardial ischemia and infarction [180, 338, 339]

IGFBP1	Promotes cell migration. High levels associate with cardiovascular disease [340-342]
ANGPTL1	A key anti-angiogenic protein (it is also known as angioarrestin) by inhibiting the proliferation, migration, tube formation, and adhesion of endothelial cells [343]
C1QTNF1	Serum levels are high in CAD and associate with CAD severity and TNFα and IL6 [344]
DCN	Ligand for multiple cell surface receptors mediates its role in tumor suppression, including a stimulatory effect on autophagy and inflammation and an inhibitory effect on angiogenesis. Cleaved from vascular endothelium by proteases [164]
SORT1	A sorting receptor in the Golgi compartment and as a clearance receptor on the cell surface. Soluble sortilin in serum/plasma associate with atherosclerosis, coronary artery disease, and peripheral arterial disease [345-347]
PCSK9	Pro-atherosclerotic effects leading to elevated levels of LDL, low HDL levels, obesity and overweight, diabetes, and coronary heart disease [348, 349]
PGF	Growth factor active in angiogenesis and endothelial cell growth. Found within human atherosclerotic lesions is associated with plaque inflammation [350]
SPARCL1	Actively released from quiescent endothelial cells via the classical secretion pathway and inhibits angiogenesis, endothelial cell proliferation and migration but required for capillary morphogenesis and integrity [351, 352]
ANGPT2	Antagonist for both ANGPT1 and TIE2, disrupts the vascular remodeling ability of ANGPT1 and may induce endothelial cell apoptosis. High in cardiovascular disease [180, 337]
COL4A1	Cleaved into arresten, comprising the C-terminal NC1 domain that inhibits endothelial cell proliferation, migration, and tube formation [353-355]. Cleaved from vascular endothelium by proteases [164]
TGFBI	Inhibit cell adhesion. Plasma TGFBI remains high in recovered COVID-19 patients [356]. Induced in various forms of heart disease affecting fibrosis and disease responsiveness [357] Cleaved from vascular endothelium by proteases [164]
PRELP	Present in connective tissue ECM. Elevated serum level in pulmonary hypertension [358] and elevated in cardiac ECM after myocardial ischemia/reperfusion injury [359]. Cleaved from vascular endothelium by proteases [164]
SPON1	Cell adhesion. Serum/plasma SPON1 significantly higher in cardiovascular disease/heart failure [13, 76, 180, 337]
IGFBP7	Binds to IGF with high affinity and stimulates cell adhesion. Roles in cardiac hypertrophy, fibrosis, cellular senescence, insulin resistance, endothelial dysfunction, and inflammation. Increase IGFBP7 reflects worsening diastolic function, adverse cardiac remodeling, metabolic derangement, and heart failure [360]. Cleaved from vascular endothelium by proteases [164]
SOD2	Mitochondrial matrix protein that clears mitochondrial reactive oxygen species, protective against apoptosis. The concentrations of plasma SOD1 and SOD2 were higher in CAD than in healthy controls [361]
NRP2	Involved in cardiovascular development, axon guidance, tumorigenesis, inflammation, and cardiovascular disease. Soluble form (sNPR2) [362] acts a decoy inhibiting function [363]
BMP4	Regulates development including heart development and adipogenesis. Role in cardiomyocyte induction [364]

GDF2	GDF2 (BMP9) binds to ACVRL1 and is potent circulating inhibitor of angiogenesis inhibiting microvascular endothelial cell migration and growth [365]
IGFBP3	Main IGF transport protein in the bloodstream. Serum levels significantly reduce during the catabolic flow phase of injury [366], acute myocardial infarction and coronary heart disease [367]
COMP	COMP is a marker of cartilage turnover, role in vascular wall remodeling [368, 369]. Cleaved from vascular endothelium by proteases [13]
PON3	Associates with HDL and inhibit the oxidation of LDL to slow the initiation and progression of atherosclerosis [370]
DKK4	Antagonist of the Wnt/β-catenin signaling pathway. Increase in blood is associated with cardiovascular disease [371]
FKBP5	FKBP5–NFκB signaling mediates inflammation, potentially contributing to cardiovascular risk [372]. Plasma level is increased in stroke patients [373]
PRSS2	Increased serum/urine levels in acute and chronic pancreatitis [374]
FBP1	Metabolism, gluconeogenesis. High serum level in acute liver failure [375]
FST	Bioneutralization of members of the TGF-β superfamily, antagonist of activin (multifunctional protein including immune response and wound repair). High Follistatin (FST) associates with COVID-19 severity and mortality reflecting local (lung and endothelium) and system damage and inflammation [376]. High in cardiovascular disease [13]
SFTPD	Pulmonary surfactant-associated protein D involved in lung's defense against inhaled microorganisms, organic antigens and toxins [377]. Leakage from the lung into circulation is a promising biomarker for lung injury [377].
LRIG1	Interact with RTKs (the EGFR family, MET and RET) as a feedback negative regulator of signaling by RTKs with role in homeostasis. Soluble form (sLRIG1) retains this inhibitor function in a paracrine manner [378]
GDF15	Inflammation, tissue hypoxia, acute injury and oxidative stress, and cardiovascular disease [13], induced in lung injury [379]
LRPAP1	Chaperon for LRP1, leakage in circulation due to tissue damage [380]. RAP Inhibits ligand binding to LDLR.
PTN	Endothelial cell migration and neovasculogenic effects in damaged heart, cardiomyocyte programmed cell death in response to pro-apoptotic stress, which may be critical to myocardial injury repair [381-383]
RSPO1	Ligand for LGR4-6 receptors activating canonical Wnt signaling by relieving the Dkk1 inhibition imposed on the Wnt pathway. Excess levels are linked to liver fibrosis [384, 385]
KRT19	KRT19 fragment (CYFRA21-1) relates to lung pathologies. Found high in severe/critical/deceased COVID-19 [386]
MATN3	Cartilage specific, role in the formation of extracellular filamentous networks. Presence in circulation my reflect tissue damage [387].
MB	Binds oxygen on a heme group. Released into the bloodstream after muscle injury [388], potential marker for heart attack [389]

HGF	Growth factor for a broad spectrum of tissues and cell types and functions. Neutrophils activation [390], liver disease [391], hypertension [392], cardiovascular [393], advanced heart failure [394], viral load and lung injury, severity and mortality in COVID-19 patients [395, 396], and immune suppression, reduced antigen presentation [397] and other suppressive effect on cytotoxic cell killing [398]
PROK1	Potently contracts gastrointestinal smooth muscle. Role in cardiovascular health and disease, marker for heart and kidney damage [399]
REG1A	Sepsis [400-402]
TINAGL1	Kidney inflammation/damage and cardiovascular damage. Cleaved from vascular endothelium by proteases [164]
GFRA1	Axon guidance/development. Co-receptor with RET for GDNF to mediate RET tyrosine kinase signaling. Released form described from neural cells and nerve injury which mediates trans signaling [403, 404]
CPA1	Acute and chronic pancreatitis [405, 406]
NEFL	Presence in plasma reflects axonal/neuronal damage [407], and stroke [408, 409]
PVALB	Muscle relaxation. Serum parvalbumin during muscle injury [410] and neural damage [411]
CPB1	Pancreatitis [412]
CTSL	Cathepsin. High serum level associates with COVID-19 severity, may play a role in SARS-CoV-2 entry; contributes to fibrosis in COVID-19 [413]. Marker of cardiovascular event [414]
CSTB	Cathepsin. Released in neutrophil NETs [104]. Reversible inhibitor of cathepsins L, H and B. Blood CSTB (Cystatin B) is a marker of cardiovascular event [414, 415]
CTSZ	Cathepsin. Cathepsin. Might contribute to fibrosis in COVID-19 [413]. Cleaved from vascular endothelium by proteases [164]
FCAR	Several functions including cytokine, proinflammatory, production. Neutrophil activation and immunity [416]. CD89 (FCAR) serves as an innate receptor during the early phase of infection [417]. Soluble form (sCD89) a biomarker for IgA nephropathy [418]
CTSD	Cathepsin. Might contribute to fibrosis in the lung, spleen, thyroid, liver, and heart in COVID-19 [413]. Cleaved from vascular endothelium by proteases [164]. Marker of cardiovascular event [414, 415]
CTSO	Cathepsin. Might contribute to fibrosis in COVID-19 [413]
CTSH	Cathepsin. Might contribute to fibrosis in COVID-19 [413]
LYVE1	Binds to hyaluronic acid (HA), cell surface receptor on lymphatic endothelial cells. Macrophage-derived LYVE-1 is shed by metalloproteinases [419] which might induce arterial stiffness and collagen deposition [420]. Shedding inhibits LYVE-1-mediated lymphangiogenic responses [421] and may promote pathological lymphangiogenesis [422]. High serum LYVE-1 during acute lower respiratory Infection and renal dysfunction [423]
EPHB4	Role in heart morphogenesis, angiogenesis and blood vessel remodeling and permeability. sEphB4 blocks activation of EphB4 and EphrinB2; suppresses endothelial cell migration, adhesion, and tube formation [424]

ROBO2	SLIT2/ROBO2 guidance cue in cellular migration, including axonal navigation and angiogenesis. Reduced sROBO2 (shedding by ADAM10 at the ectodomain) suggests low activity of the SLIT2/ROBO2 signaling [425, 426]
PLXDC1	Role in endothelial cell capillary morphogenesis [427]. Secreted form from transcript variants may act as decoy thus inhibiting capillary repair
ASGR1	Mediates the endocytosis of plasma glycoproteins; soluble form (sASGR1) [428] is upregulated in liver fibrosis/cirrhosis [429]
HSPB1	HSPB1 (HSP27) is released from platelets during activation/aggregation, and serum levels of HSP27 associate with inflammation and other tissue injuries [430, 431]
IFI30	Expressed in antigen-presenting cells and induced by INFγ in other cell types. Important in MHC class II-restricted antigen processing and restricts viral entry including SARS-CoV [432]. Secreted IFI30 (GILT) may enhance hemolysin-mediated tissue damage [433]
HMOX1	Heme catabolism. High serum/plasma levels in ARDS and interstitial lung disease [434] and acute kidney injury [435]
HMOX2	Heme catabolism. High serum/plasma levels in ARDS, interstitial lung disease, peripheral artery disease, acute kidney injury [436]
MERTK	RTK which binds to several ligands including GAS6. sMERTK act as a competitive inhibitor of MerTK by acting as a decoy for its ligand GAS6 inhibiting the anti-inflammatory function of GAS9/TAM signaling in macrophages [437, 438]. sMERTK shed during inflammatory responses and inflammatory cardiovascular lesions [437, 438], and associates with kidney disease and sepsis [439, 440]
CST3	Biomarker of kidney function [441, 442] and predicting new-onset or deteriorating cardiovascular disease [443]. sCST3 is a predictor of COVID-19 severity [444, 445]
TYMP	Role in maintaining the integrity of the blood vessels, promoting activity on endothelial cells, angiogenic activity. High serum level in sepsis [446], and associates with COVID-19 associated thrombotic event, inflammation, and organ damage [447]
SNCG	γ-Synuclein is found primarily in the peripheral nervous system. Serum/urine presence detected in cancer & secreted by cancer cells [448]. May mark peripheral nerve damage [449]
TFF2	Inhibits gastrointestinal motility and gastric acid secretion repair repairing the gastrointestinal tract [450]. Increased in serum with kidney disease [451] and declining lung function [452]
CCDC80	Cell adhesion and matrix assembly. Blood levels are linked to glucose tolerance derangements and related to inflammation-associated chronic complications in diabetes [453], and metabolic and cardiovascular risk in patients with inflammatory bowel disease [454]
CA3	Muscle specific CA released after muscle injury. Serum myoglobin/carbonic anhydrase III ratio as a marker of reperfusion after myocardial infarction [455]
SPOCK1	Cell-cell and cell-matrix interactions. Soluble form (Testican-1) is upregulated in sepsis and associates with sepsis severity [456]
TFF3	Protects the mucosa from insults, stabilizes the mucus layer and affect healing of the epithelium, repair of the intestinal mucosa and lung. Marker for lung inflammation/cancer and declining lung function [452, 457]

EZR	Linker between plasma membrane and actin cytoskeleton. Ezrin in blood could mark tissue damage, particularly the lung [458]
TACSTD2	Cell surface receptor that transduces calcium signals for self-renewal, proliferation, invasion, and survival; stem cell-like qualities. Cleaved to release the extracellular domain and the intracellular domain translocases to the nucleus; both fragments increase hyperplasia [459]. Relevant to bronchial cells/lung repair including proinflammatory secretion and hyperplasia
TGFA	Wound healing and tissue repair. TGFα has a broad mitogenic effect including epithelial development. Mediates injury-induced lung fibrosis [460]
THBS2	Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions, a ligand for CD36 mediating antiangiogenic properties [461]. High serum levels associate with fibrosis and cardiovascular diseases, heart failure and aortic aneurysm [462-467]
IGSF3	In lungs, it increased cell adhesion and decreased cell migration thus may be involved lung tissue repair [468]
AXL	Several roles in host-virus interaction and immunity. sAXL is high in severe sepsis, sepsis, and infection [440, 469]
GAS6	Ligand for AXL, secreted by endothelial cells and is important for the activation of endothelium during inflammation. High in severe sepsis, sepsis, and infection [469]
ICAM2	Interacts with EZR. Mediates adhesive interactions important for antigen-specific immune response, NK-cell mediated clearance, lymphocyte recirculation. Soluble ICAM2 (sICAM2) is elevated in endothelial dysfunction and inflammation/fibrosis [470]. Shed by platelets [91]
ICAM1	Plasma levels are predictive of COVID-19 mortality and organ failure [471]. Role in leukocyte trans-endothelial migration [472]
SOST	Negative regulator of bone growth that acts through inhibition of Wnt signaling and bone formation. Serum Sclerostin associated with ICU disease severity independent of the presence of sepsis and correlated with biomarkers reflecting renal, hepatic, and cardiac dysfunction, and biomarkers reflecting bone metabolism [473]
ITGB6	Expressed on epithelial cells, including lung. Plays key role in TGF-beta-1 activation and inflammation and lung fibrosis [474]
CDH1	Cell adhesion protein. Shedding of cleaved E-cadherin molecules during inflammatory response [475]. Blood soluble E-cadherin might reflect tissue injury in the events of inflammation [476]. Shed by platelets [91]
CD59	Potent inhibitor of the complement membrane attack complex. Soluble form has greatly reduced ability to inhibit MAC assembly on cell membranes [477]. sCD59 biomarker for glucose handling and diabetes [478], associated with cellular damage after acute myocardial infarction [479], and lung dysfunction after lung transplant [480]
MET	Wound healing, organ regeneration and tissue remodeling. Soluble c-Met relates to liver injury [481], diabetic nephropathy [482]
CD93	Cell-cell adhesion and host defense. Expressed on many cell types including platelets, neutrophils, monocytes, microglia, and endothelial cells. Soluble CD93 (sCD93) associates with CAD, acute myocardial infarction [483] inflammation [484]
DLK1	Soluble form cleaved off by ADAM17 is active in inhibiting adipogenesis neuroendocrine differentiation, reduced level associate with myocardial fibrosis [485]

FGF19	Reduced blood level in certain metabolic disorders [486], non-alcoholic fatty liver disease [487] and insulin resistance [488]. FGF19 have anti-fibrotic properties in the lung [489]
TSHB	Indispensable for the control of thyroid structure and metabolism (UniProtKB)
MSTN	Negative regulator of skeletal muscle growth. Low serum level post-myocardial infarction associate with improved survival, possibly by limiting extent of fibrosis [490]
ENPP7	Sphingomyelinase that hydrolyses sphingomyelin to ceramide in the intestinal tract. It has features to be secreted in bile and was detected in medium [491], released in intestinal lumen by bile salts and enzymes [491, 492]
SULT2A1	Enzyme in maintaining steroid and lipid homeostasis. Serum level was shown to be a marker of liver injury mouse model [493]
PTS	Metabolism; involved in serotonin biosynthesis and NO synthase activity. Induced by IL1B and INFg in endothelial cells [494]. Possibly released due to apoptosis/cell death from tissue damage.
HAO1	Oxidative stress. Located in the peroxisome and expressed in liver and pancreas [495]. Possibly released due to apoptosis/cell death from tissue damage.
MAD1L1	Mitotic checkpoint, spindle-assembly checkpoint (UniProtKB). Possibly released due to apoptosis/cell death from tissue damage.
NADK	Redox. Located in Nucleoplasm, Vesicles (the Human Protein Atlas). Possibly released due to apoptosis/cell death from tissue damage.
ANXA10	Undetermined function
CA5A	Ureagenesis and gluconeogenesis. Mitochondrial enzyme in the liver, kidney, and skeletal muscle (the Human Protein Atlas)
HEXIM1	RNA polymerase II transcription inhibitor. Regulation of innate immune response (the Human Protein Atlas)
ZBTB17	Transcription factor, prevents apoptosis in lymphoid precursors, allowing them to survive in response to IL7 and undergo proper lineage commitment (the Human Protein Atlas)
LAMP3	Also called CD208 and DC-LAMP, and almost exclusively found in matureDCs with role in dendritic cell function and in adaptive immunity, DCs maturation (the Human Protein Atlas)
CES1	Manage cellular cholesterol esterification levels and expressed in monocytes (called monocyte esterase). May be secreted in other species but no evidence in humans apart from liver cancer [496]
PRSS8	Might be an alternative entry portal for SARS-CoV-2 and contribute to and/or worsen lung infection/pneumonia [497]
NMNAT1	Nicotinamide-nucleotide adenylyltransferase (NMNAT), protective for injured axons (axon degeneration), but Inhibitory of axon regeneration (the Human Protein Atlas)
AGRP	Related to obesity [498]
KYNU	Metabolism. Biosynthesis of NAD cofactors from tryptophan through the kynurenine pathway (the Human Protein Atlas)
CD300LF	Inhibitory receptor for myeloid cells and mast cells (UniProtKB)

BLMH	Cytoplasmic cysteine peptidase. Inactivated the drug Bleomycin (UniProtKB)
ZBTB16	Transcriptional repressor and plays a role in myeloid maturation (UniProtKB)
HS3ST3B1	O-sulfation of Heparan sulfate (UniProtKB)
HS6ST1	O-sulfation of Heparan sulfate (UniProtKB)
PAPPA	Metalloproteinase which specifically cleaves IGFBP-4 and IGFBP-5, resulting in release of bound IGF. Involved in local proliferative processes such as wound healing [499]
SCARB2	Expressed in brain, heart, liver, lung and kidney, and at intercalated discs [500] & Wikipedia. Highly expressed in plasmacytoid DCs and involved in type I IFN production [501]
DFFA	Inhibitor of the caspase-activated DNase (UniProtKB)
DCBLD2	Also called ESDN, regulator of vascular remodeling and angiogenesis and inhibitor of insulin receptor signal transduction [502]
THOP1	Metabolism of peptides under 20 aa residues long, also plays a role in MHC-I antigen presentation and is secreted [503]
PILRB	Expressed on the cell surface of neutrophils, monocytes, macrophages, NK-cells, subset of T-cells and DCs. Triggering PILRB increases levels of IL-1β, TNFa and IL6 in serum or bronchoalveolar lavage fluid [504]. PILRβ is primary isoform displayed by NK cells [505]
LAYN	Cell adhesion. Upregulated in CD8+ Cytotoxic T cells [506]
DPP7	Expressed in quiescent lymphocytes (NCBI Gene)
FKBP4	Role in immunoregulatory gene expression in B- and T-Cells via IRF-4 inhibition [507]. Secreted in response to dsDNA [508]
GALNT2	Protein modification. Released by platelets [199]
PHOSPHO1	Phosphatase that has a high activity toward phosphoethanolamine (PEA) and phosphocholine (PCho). Involved in the generation of inorganic phosphate for bone mineralization (the Human Protein Atlas)
PPP3R1	Regulatory subunit of calcineurin, a calcium-dependent, calmodulin stimulated protein phosphatase (the Human Protein Atlas)
CLSTN2	Cell adhesion, modulate calcium-mediated postsynaptic signals (the Human Protein Atlas)
KLB	Bile acid synthesis and involved in activation of FGF21 protein has a protective effect on heart muscle cells [509]. Soluble, circulating form of β-klotho has been described but unclear function [510]
SLAMF8	A role in B-lineage commitment and/or modulation of signaling through the B-cell receptor (the Human Protein Atlas)
VAMP5	Participate in trafficking events that are associated with myogenesis, such as myoblast fusion and/or GLUT4 trafficking (the Human Protein Atlas)
ACVRL1	Receptor for BMP9/GDF2 and BMP10 and important regulator of normal blood vessel development (the Human Protein Atlas)
PLIN1	Perilipin, associate with the surface of lipid droplets [511]. Controls adipocyte lipid metabolism and its expression is elevated in obesity [512] Wikipedia

CD300C	Immunoregulatory. Inhibits T-cells [513]
TRIM21	TRIM21 is an intracellular antibody effector in the intracellular antibody-mediated proteolysis pathway. Involved in the regulation of innate immunity and the inflammatory response in response to IFNG/IFN-gamma [514] Wikipedia
IDUA	Heparin catabolism (the Human Protein Atlas)
AGR3	Regulation of ciliary beat frequency and mucociliary clearance in the airway, regulation of intracellular calcium in tracheal epithelial cells (UniProtKB)
PON2	Inflammation. Prevents LDL lipid peroxidation, reverses the oxidation of mildly oxidized LDL (UniProtKB)
ENAH	Induces the formation of F-actin rich outgrowths in fibroblasts (the Human Protein Atlas)
EFNA4	May play a role in the interaction between activated B-lymphocytes and dendritic cells (the Human Protein Atlas)
DRAXIN	Chemorepulsive axon guidance protein. Antagonist of Wnt signaling pathway [515]
VSIG2	Unknown
NOMO1	Part of a protein complex that participates in the Nodal signaling pathway in development (the Human Protein Atlas)
CD302	Receptor involved in cell adhesion and migration, as well as endocytosis and phagocytosis (the Human Protein Atlas)
PCDH17	Potential calcium-dependent cell-adhesion protein (UniProtKB)
PREB	A transcriptional regulator and is thought to be involved in some of the developmental abnormalities. Specifically activates the small GTPase SAR1B (UniProtKB and the Human Protein Atlas)
AHCY	Metabolism (UniProtKB)
QDPR	Enzyme for tetrahydrobiopterin biosynthesis (the Human Protein Atlas)
HSD11B1	Reduces cortisone to the active hormone cortisol (UniProtKB) that activates glucocorticoid receptors [516]
DDAH1	Regulation of nitric oxide generation, inhibit nitric oxide synthase activity (the Human Protein Atlas)
GALNT10	Protein modification (the Human Protein Atlas)
FOSB	Interacts with Jun proteins enhancing their DNA binding activities (the Human Protein Atlas)
PFDN2	A subunit of the Prefoldin complex, a chaperone complex in cytoplasm mainly involved in neurodegenerative diseases [517]
ACP6	Metabolism (UniProtKB)
CFC1	Development, vascular and heart. Maintenance of stem cells and stem cell renewal. Soluble form [518] inhibits the membrane-form function
ALDH1A1	Enzyme mainly expressed in liver (the Human Protein Atlas). Serum levels detected in cancer (e.g. breast cancer [519]). Presence in blood may be indicator of liver damage

DDC	Catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine (the Human Protein Atlas)
IGFBPL1	Axonal Guidance. Circulating protein but not characterized (the Human Protein Atlas)
ADAM22	Regulation of cell adhesion and spreading and in inhibition of cell proliferation (the Human Protein Atlas)
NTRK2	Cell differentiation (the Human Protein Atlas)
DNER	Activator of the NOTCH1 pathway. Soluble form associates with inflammation [520]
GPC5	Binds growth factors and play a role in cell division and growth regulation, and cell migration (the Human Protein Atlas). Has secreted form but not functionally characterized
PAG1	Negatively regulates T-cell antigen receptor (UniProtKB)
PRSS27	Protease mainly expressed mainly in the pancreas (the Human Protein Atlas)
BOC	Cell-cell interactions between muscle precursor cells, Promotes differentiation of myogenic cells (the Human Protein Atlas). Elevated plasma BOC in heart failure but reduced with recovery [521]
GFRA3	Axon guidance (UniProtKB)
EGLN1	Primary regulator of HIF-1α steady state levels in the cell, involved in various hypoxia-influenced processes such as angiogenesis in retinal and cardiac functionality (UniProtKB)
SIGLEC6	Immunosuppressive function on CTLs by regulating the activity of mast cells [522]
ANXA11	Midbody formation and completion of the terminal phase of cytokinesis (UniProtKB)
DSG3	Cell-cell junctions between epithelial, myocardial, and certain other cell types (the Human Protein Atlas)
USP8	Regulatory role at the level of protein turnover by preventing degradation particularly during cell cycle. Regulate T-cell anergy mediated by RNF128 (UniProtKB)
RASSF2	Promote apoptosis and cell cycle arrest (UniProtKB)
ITGA11	Integrin alpha-11/beta-1 is a receptor for collagen (UniProtKB)
LRRN1	Inhibits the Fas/FasL pathway and suppresses the apoptosis [523]
SULT1A1	Metabolism (UniProtKB)
DSG4	Cell adhesion (the Human Protein Atlas)
BID	Pro-apoptotic Bcl member (UniProtKB)
SIT1	Immunity. Negatively regulates TCR-mediated signaling in T-cells. Involved in positive selection of T-cells (the Human Protein Atlas)
NCF2	Oxidase produces a burst of superoxide which is delivered to the lumen of the neutrophil phagosome (the Human Protein Atlas)
SKAP1	Activation of T-cells, TCR signaling (UniProtKB)
F11R	Ligand for integrin ITGAL/ITGB2 to forms cell junctions and involved in the transendothelial migration of leukocytes and neutrophils [524] and platelet aggregation [525]. High level of circulating F11R in atherosclerosis [526] and hypertension [527]

SELE	E-selectin mediates in the adhesion of blood neutrophils in cytokine-activated endothelium (UniProtKB). Serum levels associate with COVID-19 severity [528, 529]. sE-selectin associates with sepsis and coagulopathy [530, 531]
SELP	P-selectin is an integral membrane protein that mediates the adhesion of activated platelets and endothelial cells to neutrophils and monocytes and has been proposed as a drug target for COVID-19-related ARDS [532]. Serum levels are higher in COVID-19 patients supporting its role in coagulopathy [533]. sP-selectin associates with sepsis and coagulopathy [530]
FCGR2A	FcγRIIa is a low affinity receptor for the Fc region of immunoglobulins gamma. Binding to IgG initiates cellular responses against pathogens and soluble antigens (UniProtKB). Relevant to immunity in COVID-19 and other infections [534]. A soluble form has been described and may modulate the interaction between immune complexes and membrane-associated Fc gamma RII [535] and shown to inhibits rheumatoid factor binding to immune complexes [536]
FCGR3B	FcγRIIIb is a low affinity receptor for aggregated and monomeric IgG. Not capable to mediate antibody-dependent cytotoxicity and phagocytosis, thus serves as a trap for immune complexes in the peripheral circulation which does not activate neutrophils ((UniProtKB)
SLAMF7	Self-receptor involved in immune modulation including NK cell-mediated cytotoxicity [537], regulation of lymphocyte adhesion [538], and in macrophage super-activation with broad implications in pathology of acute and chronic inflammation including severe COVID-19 [539]. Soluble form (sSLAMF7) has been described in multiple myeloma to activate surface SLAMF7 [540, 541]
FETUB	Protease inhibitor required for egg fertilization and other functions including systemic inflammation (the Human Protein Atlas). Reduced level of this type-3 cystatin has been reported in plasma of severe COVID-19 patients [542, 543]. Fetuin-B is a key partner in the recovery phase of an acute inflammatory response [544]
FABP4	Lipid transport protein in adipocytes. Circulating FABP4 associates with poor outcomes in cardiovascular disease, stroke and chronic kidney disease [545-547]
LTBP2	May play an integral structural role in elastic-fiber architectural organization and/or assembly [548]. LTBP2 is secreted from lung myofibroblasts in response to TGFβ1 and higher serum level in idiopathic pulmonary fibrosis patients versus healthy controls [549]
LGALS3	Galectin-3 has several roles including in innate immune responses against pathogens such as infection which leads to its secretion to act as pattern recognition protein and recruiting neutrophils [550]. In addition to its role in viral infection [551], Galectin-3 has been proposed as a biomarker for COVID-19 for its role in fibrosis and inflammation [552]
CDSN	Important for the epidermal barrier integrity (UniProtKB). Found in corneodesmosomes, which localize to human epidermis and other cornified squamous epithelia and its loss leads to skin barrier defect [553]. No literature about its presence in circulation
CNTN5	Contactins mediate cell surface interactions during nervous system development (UniProtKB)
IL22RA1	IL22RA1 and IL10RB form the receptor for IL22 and one of the receptors for IL20 and IL24 to enable signaling via JAK/STAT pathways (UniProtKB). A soluble form has been detected plasma [554]. IL22RA2 is a related homologue which is a secreted (soluble) decoy receptor for IL22 inhibiting its function [555, 556] in wound healing and in protection against microbes in non-hematopoietic cells [557]. By similarity, sIL22RA1 may be a decoy receptor for IL22
NGF	Activates cellular signaling cascades to regulate neuronal proliferation, differentiation, and survival (UniProtKB)

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