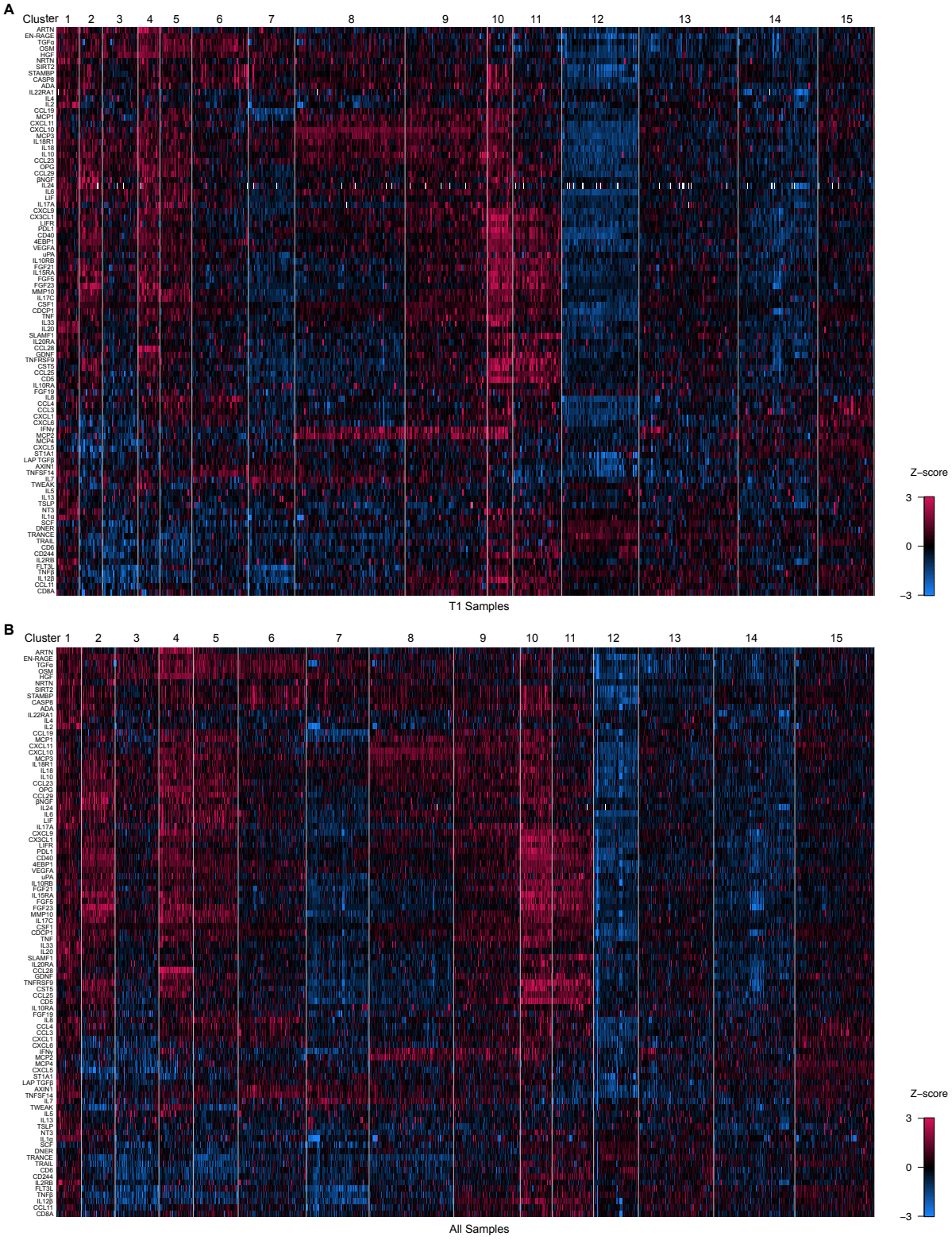
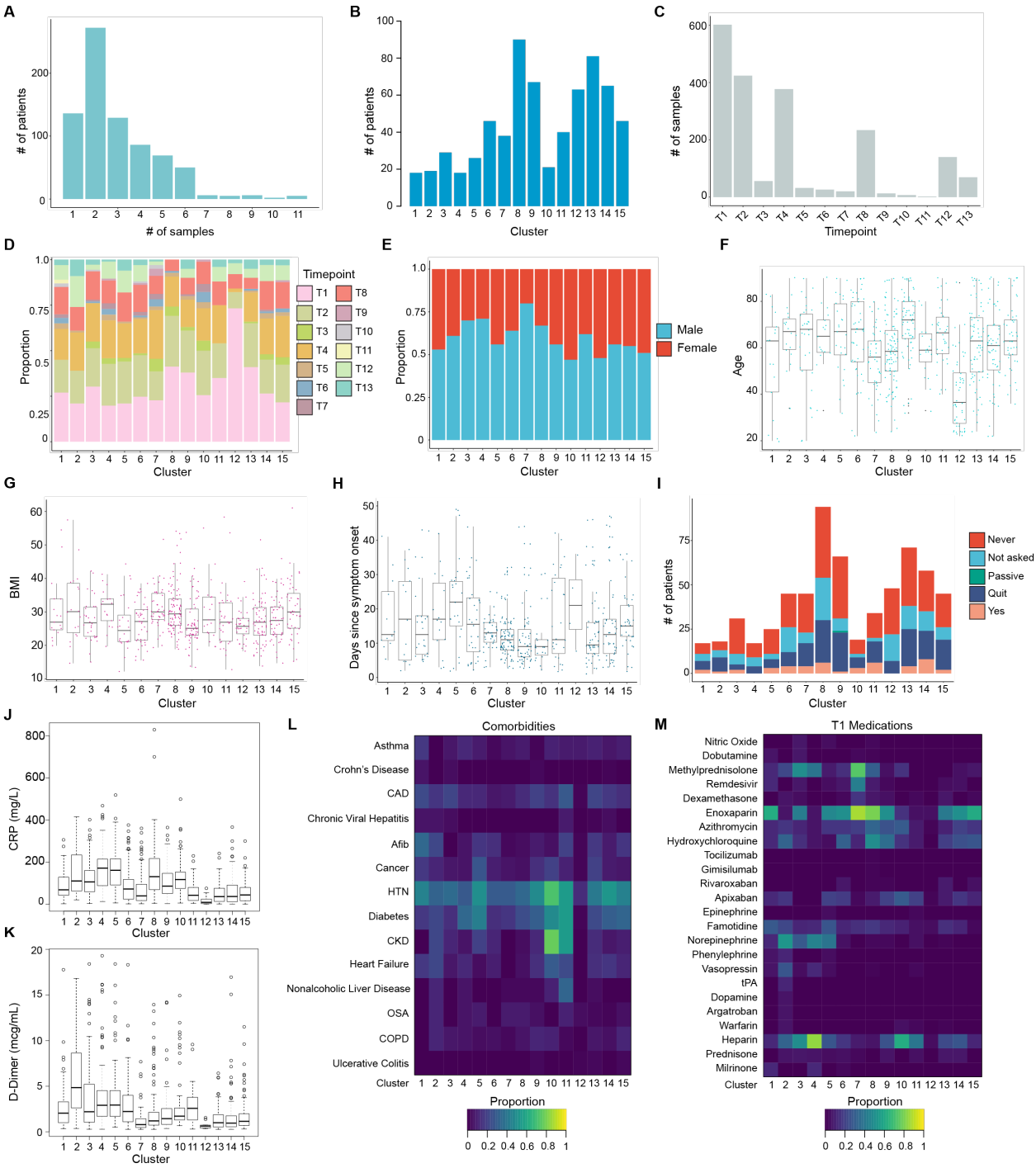
Supplementary Material

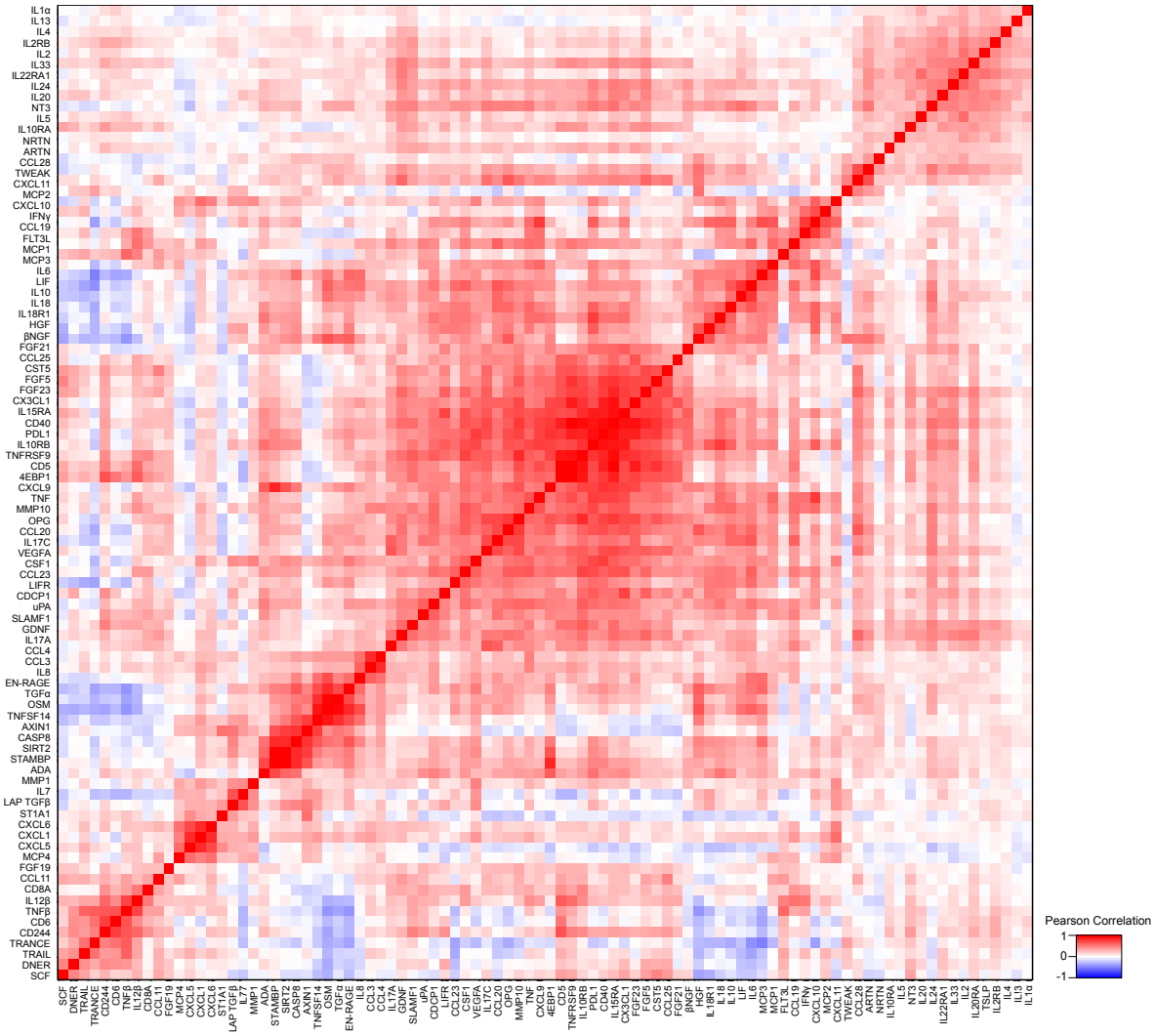


Supplementary Figure 1. Unsupervised K-means++ clustering of COVID-19 serum proteomics identified 15 distinct immune patterns (A) Heatmap showing cytokine profiles of COVID-19 sera measured with the Olink inflammation panel. Unsupervised K-means++ clustering was performed on normalized values (z-scores) for all serum samples. 15 clusters were identified. Rows denote each protein measured; columns denote proteomic profile of each patient serum sample. **(B)** Heatmap showing cytokine profiles of COVID-19 sera measured with the Olink inflammation panel. Unsupervised K-means++ clustering was performed on normalized values (z-scores) for all T1 serum samples. 15 clusters were identified. Rows denote each protein measured; columns denote proteomic profile of each patient serum sample.

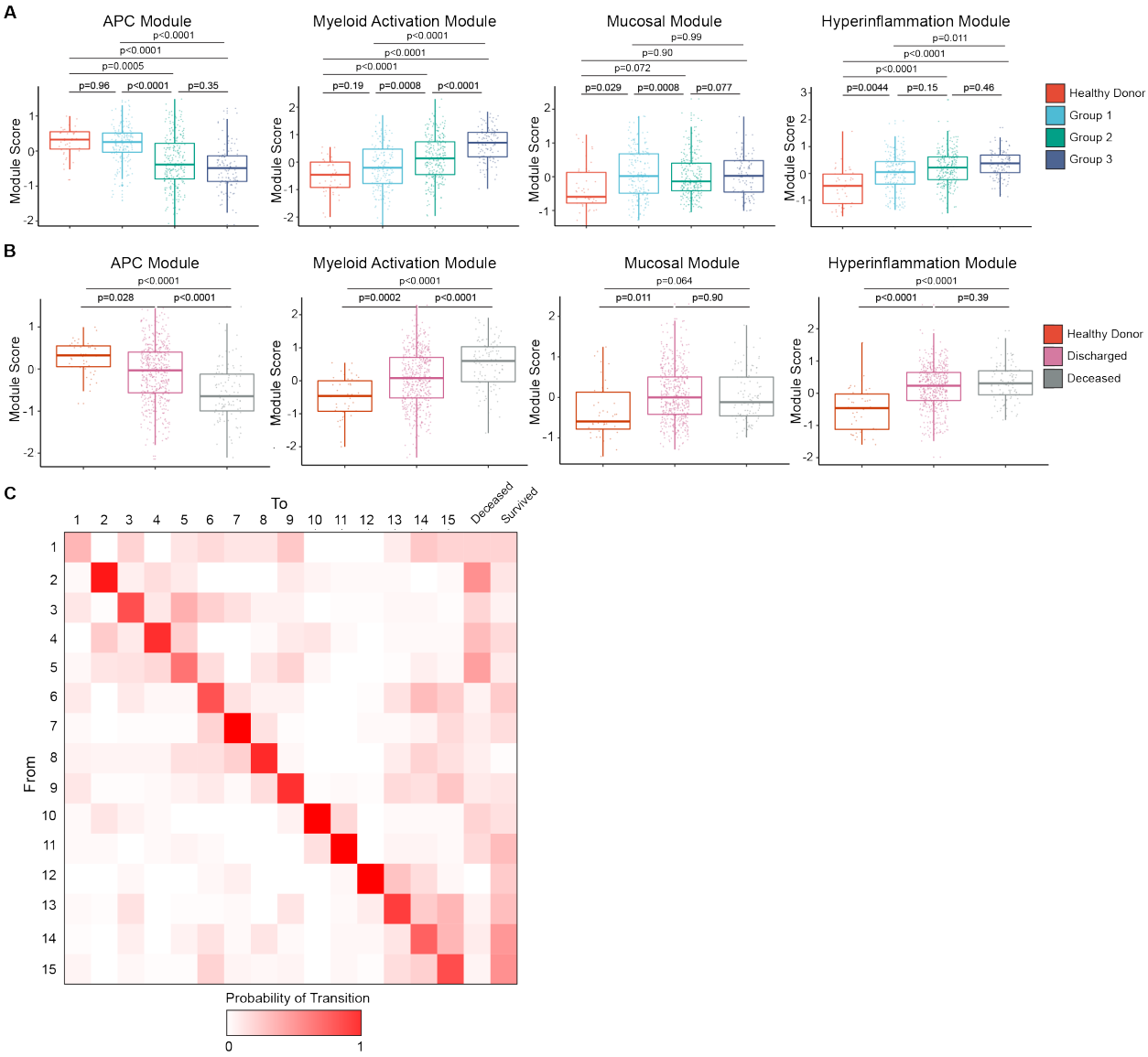


Supplementary Figure 2. Clinical characteristics of Olink serum clustering analysis. (A) Histogram showing number of patients by number of samples analyzed. **(B)** Histogram showing number of patients per Olink cluster. **(C)** Histogram showing number of samples acquired for each Timepoint. **(D)** Timepoint distribution per Olink cluster. **(E)** Proportion of sex by Olink cluster. Boxplot showing patients' age **(F)** and BMI **(G)**, and days post symptom onset **(H)** across Olink clusters. Cluster assignment set by first timepoint for each patient. **(I)** Stacked histogram showing smoking status for patients by Olink Cluster. Boxplot showing C-reactive protein **(J)** or D-Dimer levels **(K)** for first available patient samples. Cluster assignment set by first timepoint for each patient. **(L)** Heatmap showing proportion of patients with comorbidities by Olink Cluster. Cluster

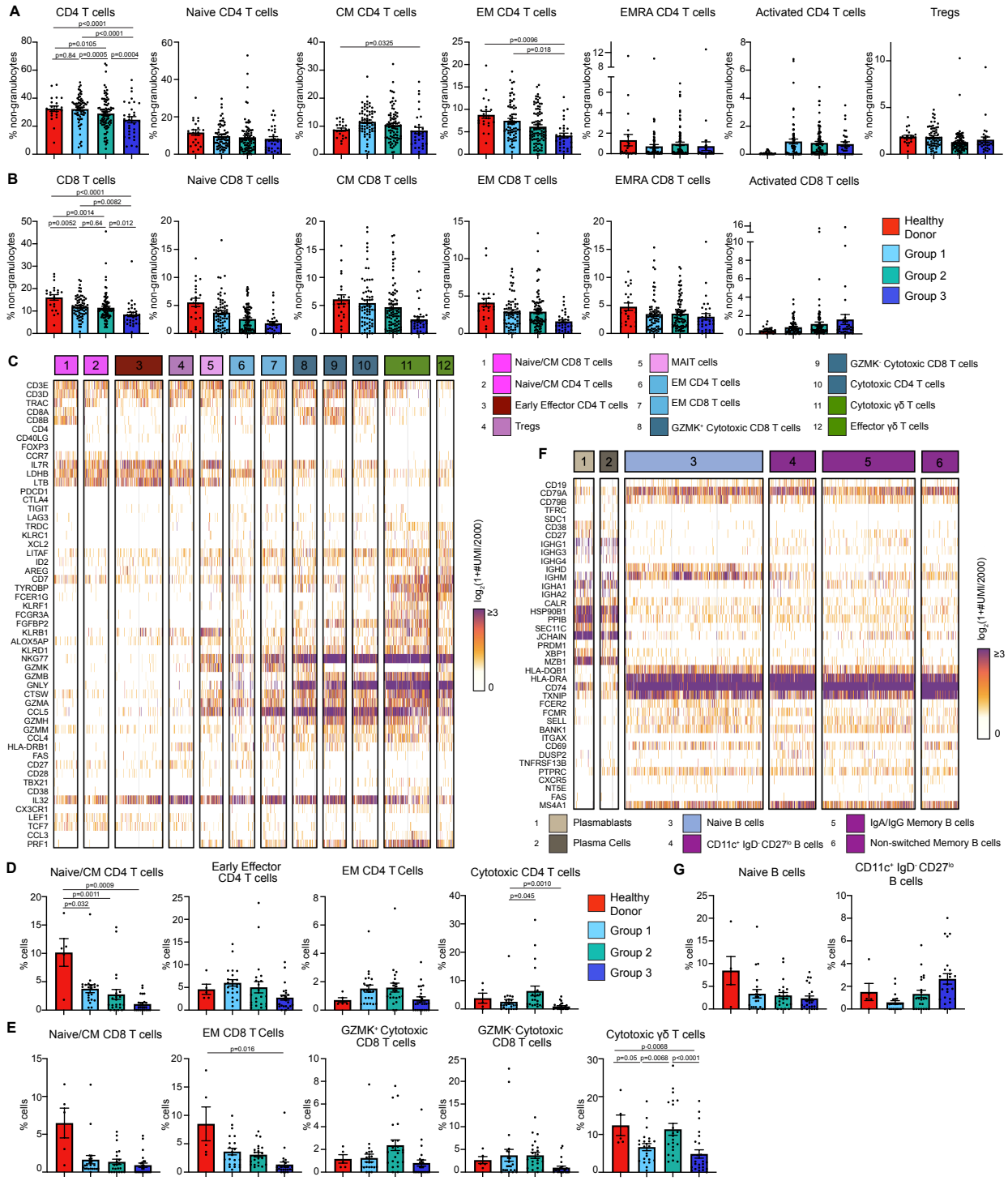
assignment set by first timepoint for each patient. **(M)** Heatmap showing proportion of patients receiving medications at time of first sampling.



Supplementary Figure 3. Covariance matrix of Olink analytes in COVID-19 serum. Heatmap showing Pearson correlations between Olink analytes for all COVID-19 patient serum samples.

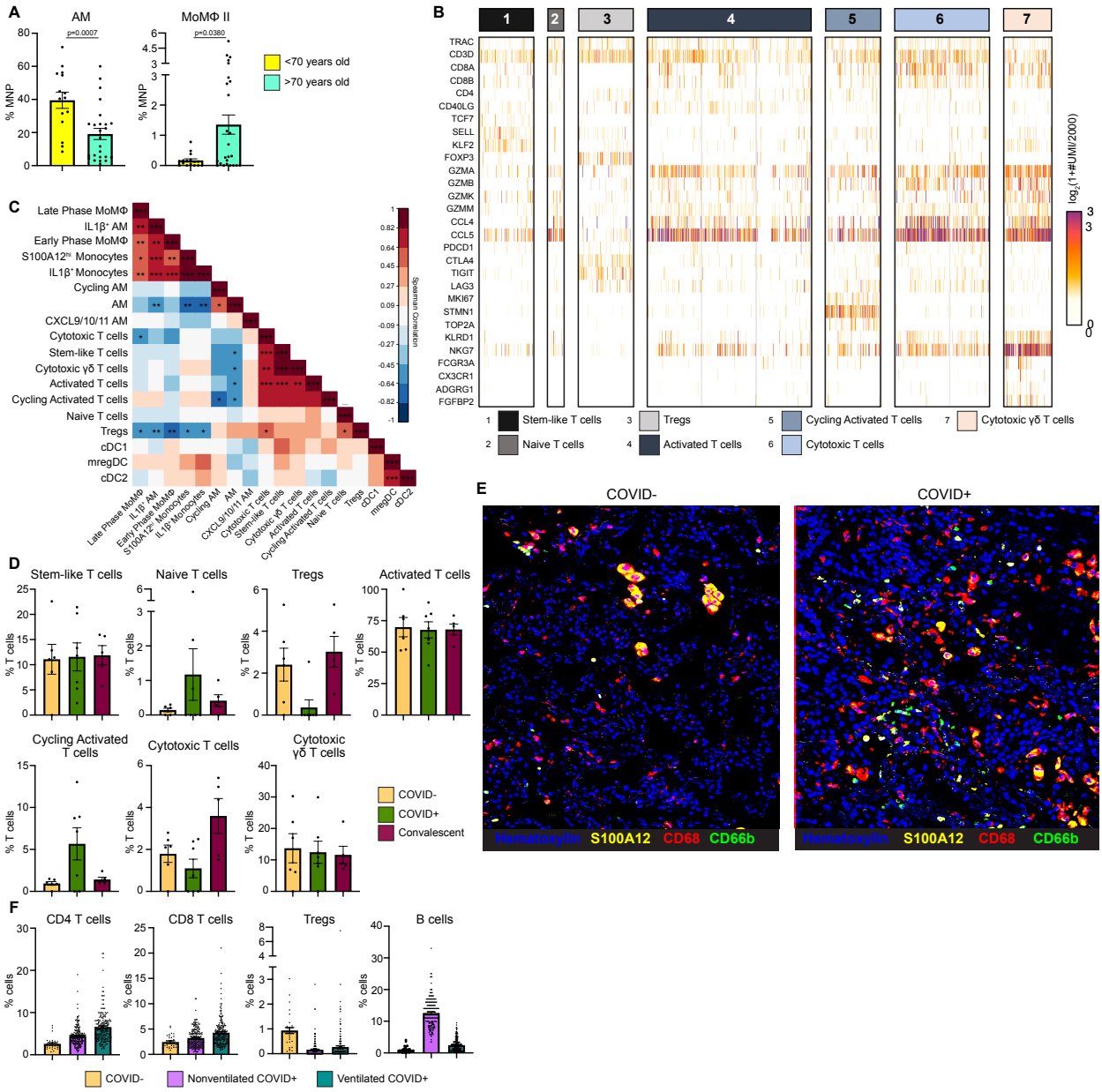


Supplementary Figure 4. Olink protein module scores are stable and associated with clinical outcome. (A) Boxplots showing Olink module score comparisons of first available serum samples by Olink group. **(B)** Boxplots showing Olink module score comparisons of first available serum samples by final clinical outcome. **(C)** Heatmap showing discrete time Markov chain analysis probability of transition between Olink clusters and clinical outcome. For box plots, each dot represents a patient sample; center line, median; box limits, 25th and 75th percentile; whiskers, 1.5x IQR. Statistical significance (**A-B**) determined by 2-way ANOVA with Tukey's Multiple Comparisons correction. Adjusted p-values shown.



Supplementary Figure 5. High dimensional characterization of circulating lymphocytes in COVID-19. CD4 **(A)** and CD8 **(B)** T cell population frequencies (% non-granulocytes) in whole blood by Olink group measured by CyTOF. **(C)** Heatmap showing UMI counts of selected genes from T cell scRNAseq clusters from PBMC. Cell frequencies shown as % cells for select CD4 **(D)**, CD8 and γδ T cell **(E)** scRNAseq clusters. **(F)** Heatmap showing unique molecular identifier (UMI) counts of selected genes from B cell scRNAseq clusters from PBMC. **(G)** scRNAseq cell

frequencies shown as % cells for select B cell clusters. For bar graphs, each dot (**A-B, D-E, G**) represents a patient sample. Statistical significance (**A-B, D-E, G**) determined by 2-way ANOVA with Holm-Sidak multiple comparisons correction. Adjusted p-values shown.



Supplementary Figure 6. High dimensional characterization of immune cells in BAL (A) AM and MoMΦ II frequencies as % MNP from scRNAseq analysis of normal lung tissue from untreated early stage non small cell lung cancer patients. Each dot represents single patient sample. Statistical significance determined by Mann-Whitney test. **(B)** Heatmap showing UMI counts of selected genes from T cell scRNAseq clusters from BAL. **(C)** Matrix of spearman correlation coefficients between identified scRNAseq BAL clusters. *p<0.05, **p<0.005, ***p<0.0005. **(D)** scRNAseq T cell cluster frequencies as % T cells from BAL. Each dot represents a patient sample **(E)** Overlaid, pseudocolored MICSSS image of $COVID^+$ and $COVID^-$ lungs, staining for S100A12, CD68, CD66b, and Hematoxylin. Granulocyte-like cells defined as $CD66b^+$ cells. **(F)** Quantification of lymphocytes in MICSSS images, shown as % cells. CD4 T cells defined as $CD3^+$ $CD8^-$ cells, CD8 T cells defined as $CD3^+$ $CD8^+$ cells, Tregs defined as $CD3^+$ $CD8^-$ $Foxp3^+$ cells, B cells defined as $CD20^+$ cells.

Supplementary Table 1. Mount Sinai COVID-19 Biobank Cohort. IQR, Interquartile Range; EOD, end organ damage; CyTOF, cytometry by time of flight; scRNAseq, single cell RNA sequencing

	COVID+	**COVID-**
Number of Subjects	583	45
Age (Median (IQR))	63 (53-74)	36 (26-47)
Male Sex (%)	61.2%	46.7%
Deceased	17.7%	0.0%
COVID-19 clinical severity at time of first sample		
Moderate COVID-19	61.1%	
Severe COVID-19	22.8%	
Severe COVID-19 with EOD	12.3%	
N/A	3.8%	

Supplementary Table 2. Mount Sinai Hospital Disease Severity Classification. SpO_2, oxygen saturation; CXR, chest X-ray; CrCl, Creatinine Clearance; ALT, Alanine aminotransferase; ULN, upper limit of normal; RRT, renal replacement therapy

Disease Severity	
Moderate COVID-19	SpO_2<94% on RA or pneumonia by CXR, ≦6 L/min O2 support
Severe COVID-19	>6L/min O_2 support, (-) pressors, CrCL>30 mL/min, ALT<5x ULN
Severe COVID-19 with EOD	>6 L/min O_2 support, (+) pressors, CrCl<30 mL/min or new RRT or ALT>5x ULN

Supplementary Table 3. Clinical information for PBMC scRNAseq samples. PSO, post symptom onset; HD, healthy donor; EOD, Severe COVID-19 with End Organ Damage; CKD, chronic kidney disease

Subject ID	**Timepoint**	**Age**	**Sex**	**Days PSO**	**Disease severity**	**Olink Group**	**Olink Cluster**	**Final Clinical Outcome**
PICR8016	T1	28	M	n/a	HD	n/a	n/a	Survived
PICR8017	T1	25	F	n/a	HD	n/a	n/a	Survived
PICR8106	T1	58	M	n/a	HD	1	12	Survived
PICR8107	T1	56	F	n/a	HD	1	12	Survived
PICR8108	T1	50	F	n/a	HD	n/a	n/a	Survived
PICR8109	T1	51	M	n/a	HD	n/a	n/a	Survived
PICR7250	T1	68		n/a	n/a	1	15	Deceased
PICR7161	T1	65	M	7	EOD	2	9	Survived
	T12			19	Moderate	1	13	
PICR7247	T1	65	F	3	Moderate	1	13	Survived
	T4			8	Moderate	1	14	
PICR7114	T1	80	M	32	EOD	2	6	Survived

	T4			35	Moderate	1	13	
	T8			39	Moderate	1	15	
PICR7393	T1	83	F	16	Severe	1	13	Survived
	T4			19	Moderate	2	6	
PICR7061	T12	89	M	19	Severe	1	13	Survived
PICR7389	T1	39	F	28	Moderate	1	14	Survived
PICR7321	T1	59	M	12	Moderate	1	14	Survived
	T4			15	Moderate	2	7	
	T8			21	Moderate	1	14	
PICR7481	T13	68	M	37	Moderate	1	14	Survived
PICR7189	T4	39	M	16	Severe	1	15	Survived
	T8			20	Severe	1	15	
PICR7162	T4	47	F	11	Severe	1	15	Survived
	T8			16	Severe	1	15	
PICR7292	T4	53	M	8	Moderate	1	15	Survived
PICR7059	T1	66	M	5	Moderate	2	8	Survived
	T4			8	Severe	2	8	
	T12			17	Moderate	2	8	
	T13			27	Moderate	1	15	
PICR7068	T4	69	F	20	Moderate	1	15	Survived
PICR7276	T12	71	M	17	Severe	1	15	Survived
PICR7066	T1	70	M	11	Moderate	2	8	Survived
	T4			17	n/a	n/a	n/a	
PICR7420	T1	78	M	29	Moderate	2	6	Deceased
PICR7146	T1	50	F	17	Severe	2	8	Deceased
PICR7218	T1	89	F	18	Moderate	3	5	Survived
	T4			21	Moderate	2	6	
PICR7403	T1	20	M	5	EOD	3	3	Survived
	T4			9	Moderate	2	7	
	T8			12	Moderate	2	7	
PICR7070	T1	70	M	n/a	Moderate	2	7	Survived
	T4			n/a	Moderate	2	7	
PICR7484	T1	66	M	9	Severe	2	8	Survived
	T12			21	EOD	3	5	
PICR7063	T1	69	M	16	Severe	2	8	Survived
	T8			23	EOD	3	5	
PICR7333	T1	32	M->F	7	Severe	2	9	Survived
	T4			13	Severe	3	1	
PICR7158	T1	69	F	7	Moderate	2	9	Survived
	T4			10	EOD	3	4	
	T12			20	EOD	3	4	
	T13			29	EOD	2	9	
PICR7294	T8	80	M	21	Moderate	2	9	Survived
PICR7073	T1	47	M	23	EOD	CKD	10	Deceased
	T4			26	EOD	CKD	11	
	T8			30	EOD	3	2	
	T12			37	EOD	3	2	
PICR7363	T8	74	F	n/a	EOD	3	5	Deceased
PICR7125	T1	94	F	10	EOD	3	2	Deceased

PICR7239	T1	68	F	14	Severe	3	3	Deceased
PICR7405	T4	84	F	n/a	EOD	3	5	Deceased
PICR7292	T1	53	M	5	Moderate	3	1	Survived
PICR7091	T4	66	F	9	EOD	3	2	Survived
	T8			12	Moderate	3	2	
	T12			16	Moderate	3	4	
PICR7476	T1	70	F	3	EOD	3	4	Survived
	T4			6	Moderate	3	2	
PICR7173	T1	65	M	24	EOD	3	3	Survived
	T4			27	EOD	3	3	
PICR7175	T4	69	F	6	EOD	3	4	Survived
	T8			11	EOD	3	4	
	T12			21	Severe	3	3	
	T13			25	Severe	CKD	11	
PICR7224	T4	59	F	16	Moderate	CKD	10	Deceased
	T8			20	Moderate	CKD	10	
	T12			23	Moderate	CKD	10	
PICR7178	T1	33	F	9	Moderate	CKD	10	Survived
PICR7266	T4	57	F	36	Moderate	CKD	11	Survived
	T8			40	Moderate	CKD	11	

Supplementary Table 4. Clinical information for BAL samples. PSO, post symptom onset; PI, post intubation

Subject ID	COVID Status	Outcome	Days PSO	Days PI	Age	Sex
PICR7406	+	Deceased	10	2	77	F
PICR7386	+	Survived	17	2	56	M
PICR7295	+	Deceased	46	15	51	M
PICR7022	+	Survived	41	2	51	M
BAL8010	+	Deceased	22	1	72	M
BAL8014	+	Deceased	18	0	94	F
BAL8020	+	Survived	21	3	51	F
BAL8007	-	Survived			61	F
BAL8008	Convalescent	Survived			44	M
BAL8009	Convalescent	Survived			51	M
BAL8011	-	Survived			70	F
BAL8012	-	Survived			65	M
BAL8016	-	Survived			61	M
BAL8017	-	Survived			53	M
BAL8021	Convalescent	Survived			72	M
BAL8022	-	Survived			59	M
BAL8024	Convalescent	Survived			61	M
BAL8027	Convalescent	Survived			62	F

Supplementary Table 5. Clinical Information for lung autopsy samples. PMI, post mortem interval; PSO, post symptom onset; AHRF, acute hypoxic respiratory failure; 2/2, secondary to

Subject ID	Age	Sex	PMI (hours)	Days PSO	Days hospitalized	Intubated	Cause of Death
MA-20-120	59	F	5.5	13	8	No	AHRF 2/2 COVID-19
MA-20-149	77	F	7.5	25	22	Yes	AHRF 2/2 COVID-19
MA-20-123	61	M	3	29	48	Yes	AHRF 2/2 COVID-19
MA-20-81	57	F	N/A	4	4	No	AHRF 2/2 COVID-19