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**

| Disease                         | Percentage |
|---------------------------------|------------|
| 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                          | Criteria                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------|
| Moderate COVID-19                          | SpO$_2$<94% on RA or pneumonia by CXR, ≤6 L/min O$_2$ 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      | HD               | 1           | 15           | Deceased              |
| PICR7161     | T1        | 65  | M   | 7        | EOD              | 2           | 9            | Survived              |
| T12          |           |     |     |          |                  | 1           | 13           |                       |
| PICR7247     | T1        | 65  | F   | 3        | Moderate         | 1           | 13           | Survived              |
| T4           |           |     |     |          |                  | 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 |
### Supplementary Table 4. Clinical information for BAL samples.

| 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.

| Subject ID | COVID Status | Outcome  | Days PSO | Days PI | Age | Sex |
|------------|--------------|----------|----------|---------|-----|-----|
| PICR7476   | T1           | 70 F     | 3        | EOD     | 3   | 4   | Survived |
| PICR7173   | T1           | 65 M     | 24       | EOD     | 3   | 3   | Survived |
| PICR7175   | T4           | 69 F     | 6        | EOD     | 3   | 4   | Survived |
| PICR7224   | T4           | 59 F     | 16       | Moderate| CKD 10 | Deceased |
| PICR7178   | T1           | 33 F     | 9        | Moderate| CKD 10 | Survived |
| PICR7266   | T4           | 57 F     | 36       | Moderate| CKD 10 | Survived |

**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 |