**TITLE:** Key patient demographics shape innate immune topography in non-critical hypoxic COVID-19 pneumonia

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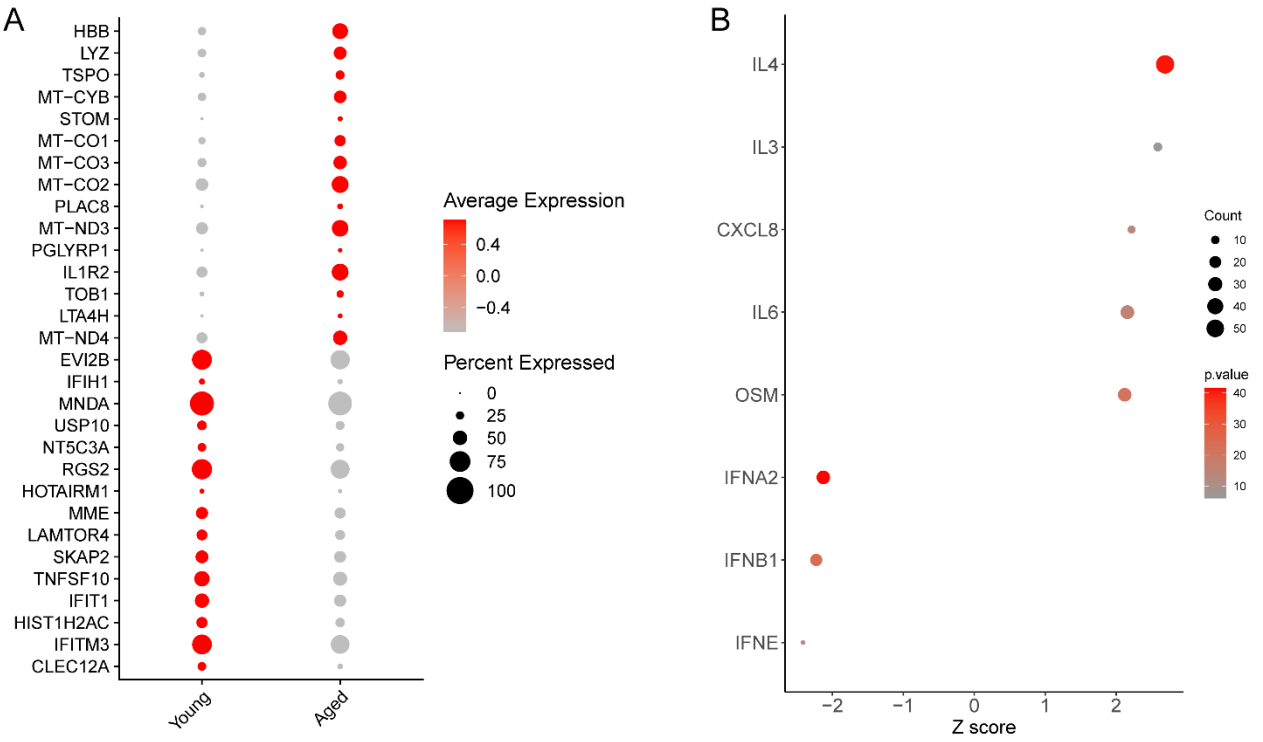
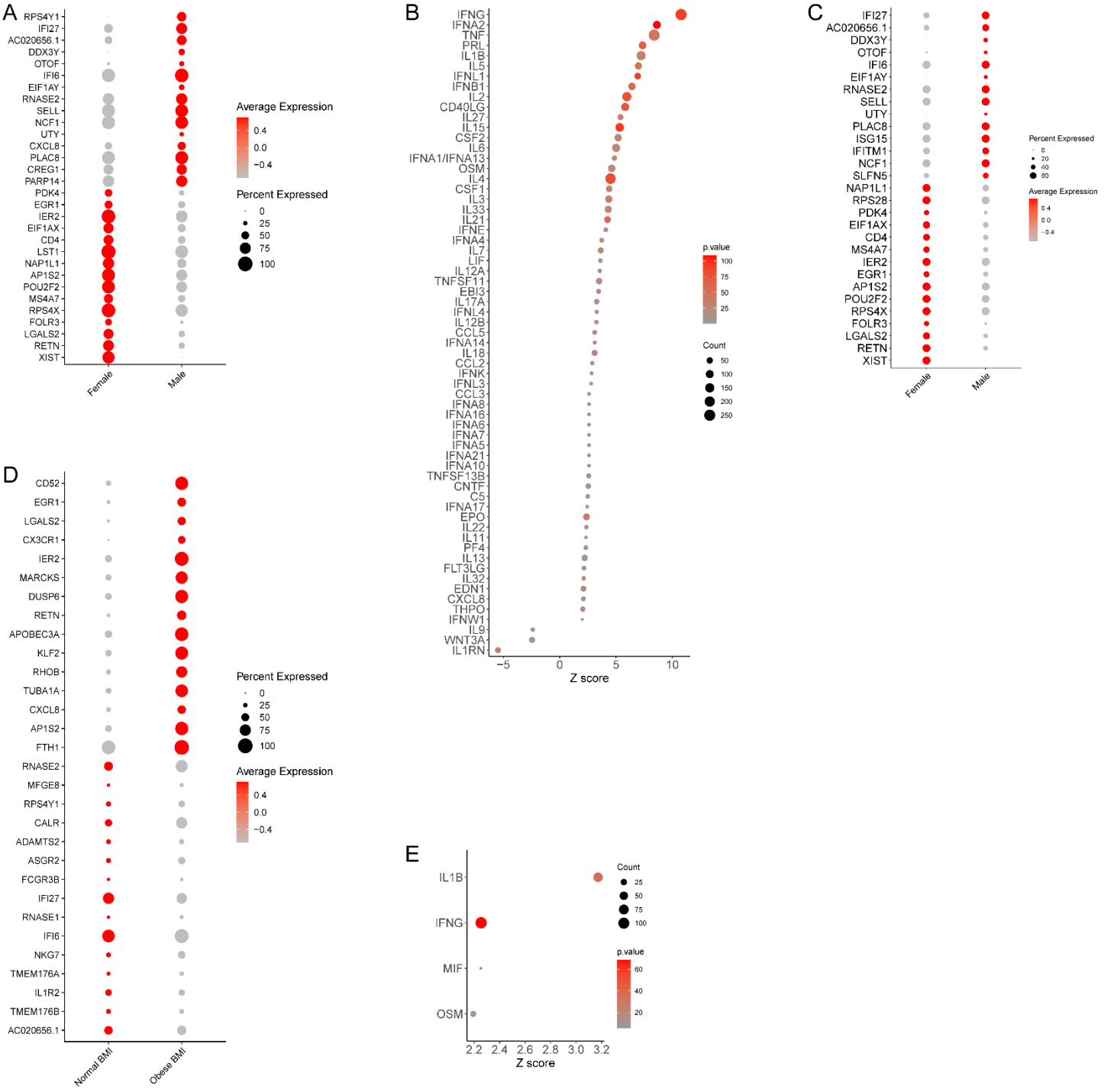
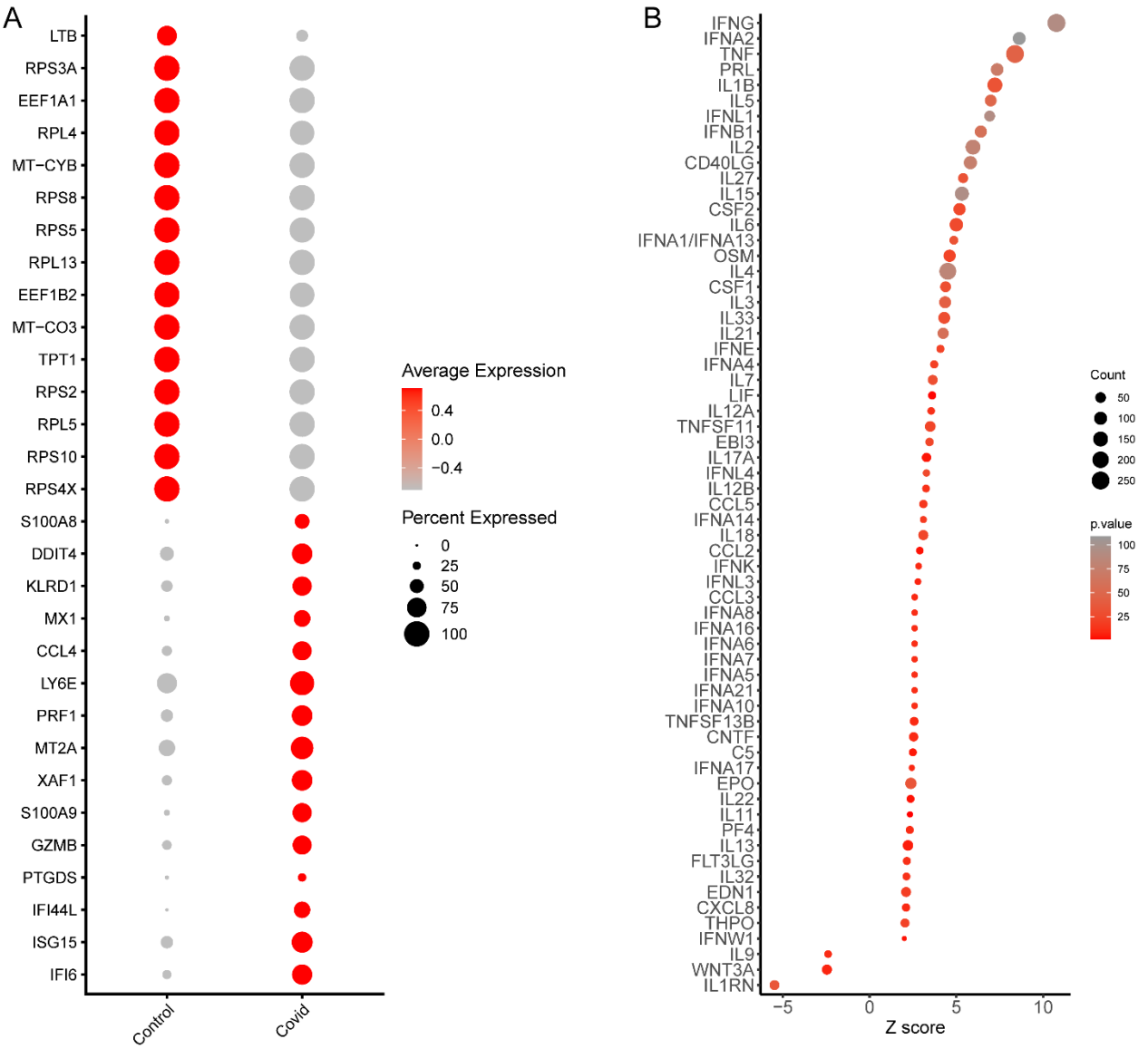
**SUPPLEMENTAL MATERIAL:**



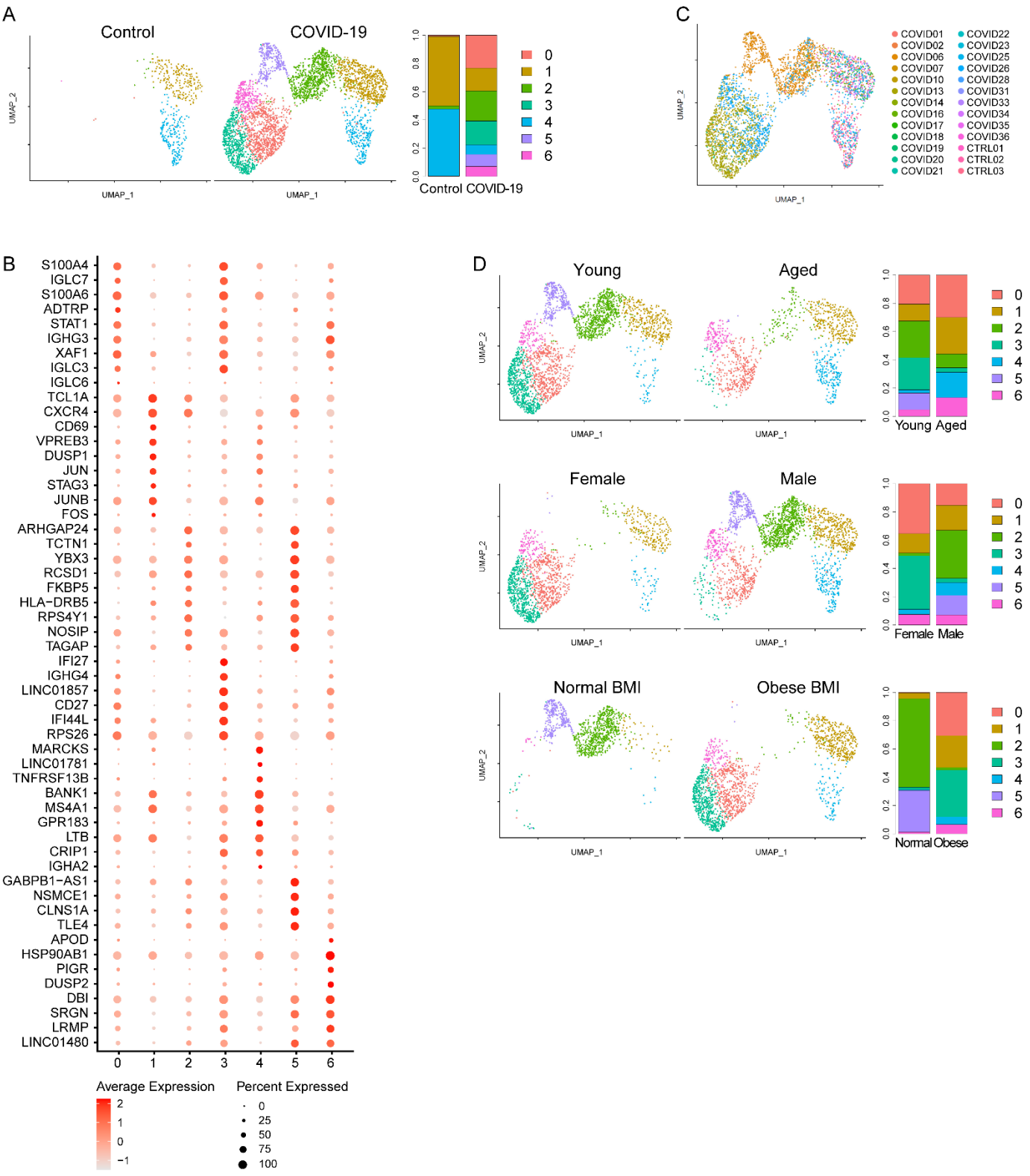

**Supplemental Figure 1. Neutrophil DEGs reveal dysregulated interferon (IFN) responses in COVID-19 age comparison. A.** Top differentially expressed genes (DEGs) in neutrophils from aged (65 years of age and older) and young (<65 years of age) COVID-19 patients ranked by fold change. **B.** Upstream regulators significantly (|z-score|≥2) activating the aged transcriptional signature in COVID-19 patient neutrophils ranked by z-score (positive, activated in aged; negative, inhibited in aged).



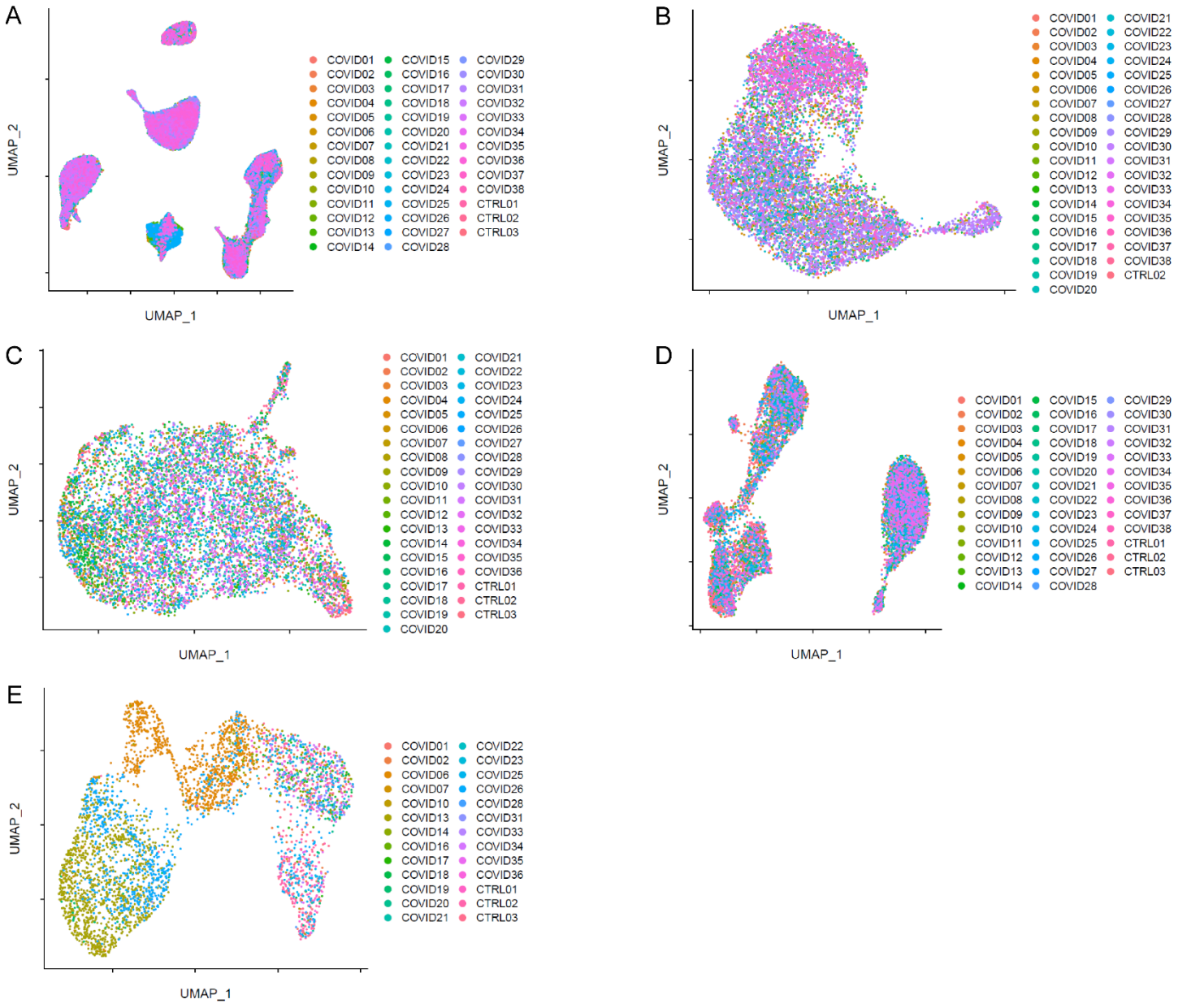

**Supplemental Figure 2. Monocyte/dendritic cell DEGs reveal distinct transcriptional COVID-19 risk signatures. A.** Top 15 DEGs in Mo/DCs from male and female COVID-19 patients ranked by log(fold change). **B.** Upstream regulators significantly activating and inhibiting the male-biased transcriptional signature in COVID-19 patient Mo/DCs ranked by z-score (positive, activated in male; negative, inhibited in male). **C.** Top 15 DEGs in CD14+ monocytes from male and female COVID-19 patients ranked by log(fold change). **D.** Top 15 DEGs in Mo/DCs from COVID-19 patients with obese and normal body mass index (BMI) patients ranked by log(fold change). **E.** Upstream regulators significantly activating and inhibiting the obese BMI-biased transcriptional signature in COVID-19 patient Mo/DCs ranked by z-score (positive, activated in obese; negative, inhibited in obese).




**Supplemental Figure 3. T/NK cell DEGs show increased ISGs, cytotoxic granular factors, and S100 genes in COVID-19 versus control patient comparison. A.** Top differentially expressed genes (DEGs) in T/NK cells from COVID-19 versus control patients ranked by fold change. **B.** Upstream regulators significantly (|z|≥2) activating the COVID-19 disease transcriptional signature in T/NK cells ranked by z-score (positive, activated in COVID-19 patients; negative, inhibited in COVID-19 patients).




**Supplemental Figure 4. B cell sub-clustering identifies three COVID-19 patients with B cell expansion. A.** UMAP plot of 4,247 B cells colored by sub-cluster and split by disease state. Bar plot, proportion of cells in each sub-cluster split by disease state. **B.** Dot plot of representative marker genes for each B cell sub-cluster. Color scale, average marker gene expression. Dot size, percentage of cells expressing marker gene. **C.** UMAP plot of B cells colored by donor. **D.** UMAP plots and bar plots of B cells split by risk factor subgroup. Only COVID-19 patient cells from the indicated risk factor subgroups are presented on each plot.




**Supplemental Figure 5. UMAP plots of each leukocyte type colored by donor.** The B cell panel is replicated as **Supplemental Figure 4C**.

[See .xlsx file]

**Supplemental Table 1. COVID-19 patient characteristics.** For comorbidity and past medical history data as well as dexamethasone therapy data, a value of 0 indicates no and a value of 1 yes. ICD-10 codes extracted for comorbidity and past medical history data are available in **Supplemental Table 4**.

| | | Neutrophil | Monocyte/DC | T/NK cell | B cell | Platelet |
|---|---|---|---|---|---|---|
| | Control | 45 | 952 | 2920 | 438 | 439 |
| COVID-19 patients | COVID-19 | 10978 | 7468 | 7919 | 869 | 964 |
| | Young | 5720 | 3685 | 3867 | 416 | 593 |
| | Aged | 5258 | 3783 | 4052 | 453 | 371 |
| | Female | 3830 | 2333 | 2573 | 266 | 452 |
| | Male | 7148 | 5135 | 5346 | 603 | 512 |
| | Normal BMI | 1616 | 1235 | 564 | 50 | 124 |
| | Obese BMI | 6989 | 4850 | 4914 | 532 | 634 |

**Supplemental Table 2. Cell counts for the indicated subgroups within each cell type.** Grey shading indicates comparisons lacking an adequate cell count (<100 cells for either subgroup) for DEG calculation. Control patient cells are represented only in the Control row. All other counts represent only COVID-19 patient cells (indicated by the thick border). B cell values reflect counts after exclusion of three outliers as discussed in the text. DC, dendritic cell; NK, natural killer.

[See .xlsx file]

**Supplemental Table 3. Differentially expressed genes (DEGs) for each cell type across the indicated comparisons.** Risk factor subgroups show numbers of DEGs only among COVID-19 patient cells. DEGs are adjusted for covariates of age, sex, BMI, and race (excluding the covariate being examined).

[See .xlsx file]

**Supplemental Table 4. ICD-10 codes used for extraction of comorbidity and past medical history data in Supplemental Table 1.**

[See .xlsx file]

**Supplemental Table 5. Cell counts for each donor for each labeled cell type.**