## Supplemental material

Fig. S1 – S5

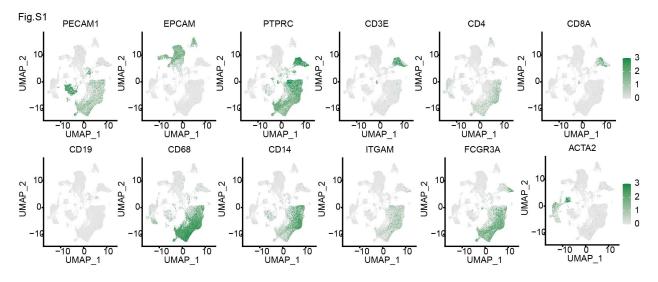


Figure S1. Uniform manifold approximation projecting distribution of signature genes in 251,612 single cells.

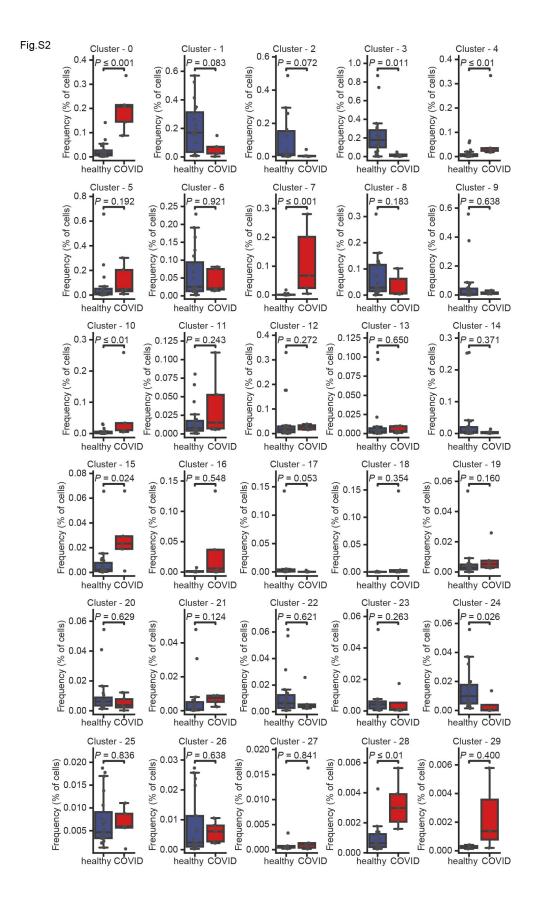


Figure S2. 29 cell clusters plotted as frequency of total cells between healthy and COVID lung tissues for the respective genes as indicated. Each dot represents an individual human subject. 5 COVID patients and 20 healthy controls were assessed. Data are expressed as mean  $\pm$  SD, Data were analyzed by two-tailed unpaired t-test, *P* values were labeled.

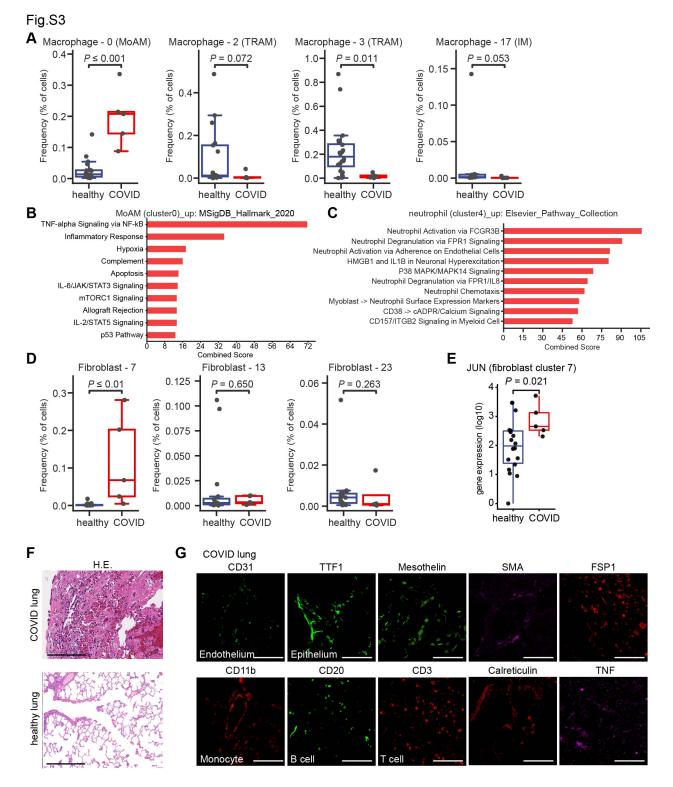


Figure S3. Profiling of major cell population in the lung of COVID patients.

A. Dot plots of macrophage abundance in lung tissues from COVID patients or healthy subjects (clusters 0, 2, 3, 17) MoAM: monocyte derived alveolar macrophage; TRAM: tissue resident alveolar macrophage; IM: interstitial macrophage.

B-C. MSigDB algorythm identified activated pro-inflammation signaling in MoAM (cluster 0) as well as inflammatory cell activation with Elsevier pathway collection analysis in neutrophil (cluster 4).

D. Dot plots of fibroblast subsets (clusters 7, 13, 23 in percentage) in diseased lung tissues from COVID-19 patients or healthy lungs.

E. Box plots showing change of JUN expression levels in cluster 7 (fibroblasts) relative to healthy controls.

F. Representative H.E. images of lung histology from COVID patient.

G. Immunofluorescence staining of lung histology from COVID patient.

Scale bar: 100  $\mu$ m. Data are expressed as mean ± SD of 5 patients with COVID-19 and 20 healthy subjects. Data were analyzed by two-tailed unpaired t-test, *P* values as indicated.



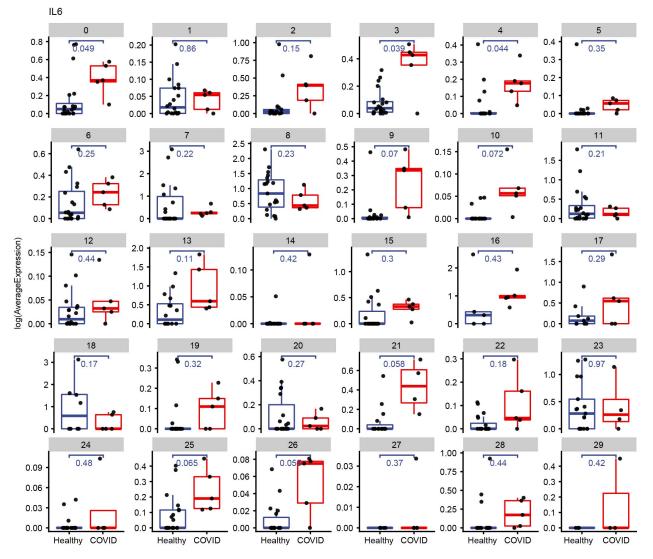


Figure S4. The expression of IL-6 in all clusters demonstrates increased IL6 expression in COVID patients in clusters 0, 3, 4, 9 and 26 compared to healthy lung cohorts.

Fig.S5

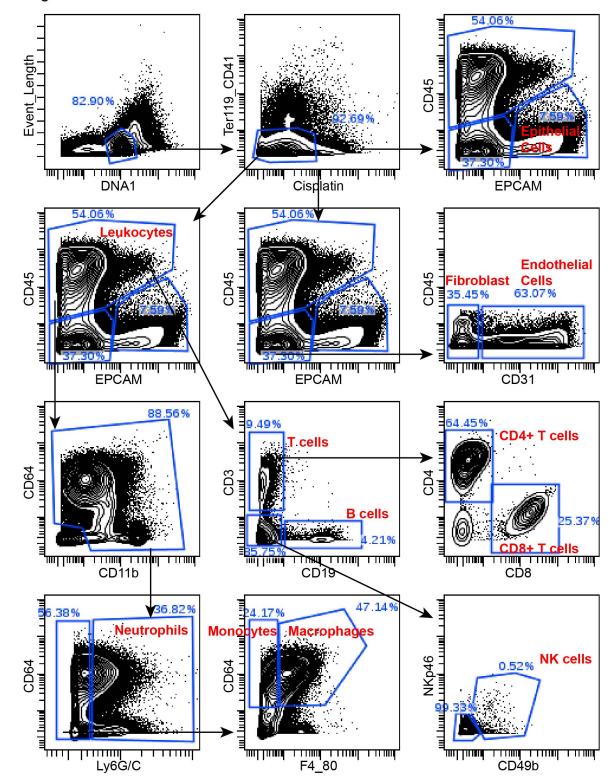


Figure S5. Gating strategy applied to determine different cell lineages.

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