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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	no software was used for data collection
Data analysis	1. Terra, a Cloud platform for storing and sharing data and analysis, tools; https://app.terra.bio/ 2. Cumulus/cellranger_workflow on Cumulus, a (cloud-based) framework for running cellranger mkfastq and cellranger counts; used to run cellranger counts, version run was Snapshot 10 on Terra ;Read the Docs: https://cumulus.readthedocs.io/en/latest/cellranger.html; Terra WDL: https://portal.firecloud.org/?return=terra#methods/cumulus/cellranger_workflow/10 3. SARS-CoV-2 genome , used to align viral reads. Transcriptome reference name: BetaCov/South Korea/KCDC03/2020 based on NC_045512.2 https://github.com/hyeshik/sars-cov-2-transcriptome 4. Cumulus/cumulus workflow on Cumulus, a (cloud-based) framework for high-throughput single cell and single nucleus analysis using Pegasus; used for quality control and clustering analysis on individual samples, version run was Snapshot 29 on Terra; Read the Docs: https://cumulus.readthedocs.io/en/latest/cumulus.html# ; Terra WDL: https://portal.firecloud.org/?return=terra#methods/cumulus/cumulus/29 5. CellBender remove-background, removes ambient RNA and other technical artifacts from count matrices, version 0.2.0. Read the Docs: https://cellbender.readthedocs.io; Terra WDL: cellbender/remove-background (snapshot 11) Terra WDL: https://portal.firecloud.org/#methods/cellbender/remove-background/11 6. Scanpy, Python package for scRNA-seq data handling/processing, version 1.5.1+1.5.2.dev5+ge5d246aa; https://scanpy.readthedocs.io 7. Harmony-Pytorch, Python implementation of Harmony batch correction method, version 0.1.3; https://github.com/lilab-bcb/harmony-pytorch 8. Pegasus, Python package for scRNA-seq data handling/processing and generating heatmaps for NanoString GeoMx data, version 0.17.2; 1.0.0; https://pegasus.readthedocs.io 9. DESeq2, R package for analysis differential gene expression,version 1.28.0 for bulk RNA seq analysis, version 1.30.0 for viral and spatial DE analysis http://bioconductor.org/packages/release/bioc/html/DESeq2.html 10. MuSiC, R package for estimation of cell type proportions in bulk RNA-seq data, version 0.1.1; https://github.com/xuranw/MuSiC 11. GSEA, software for analyzing gene set enrichments, version 4.1.0 (run with database available as of 11/1/2020); https://www.gsea-

msigdb.org/gsea/index.jsp
12. GeoMx NGS Pipeline (DND) Processing Nanostring GeoMx NGS data for WTA and CTA assays, version 1.0.0; https://blog.nanostring.com/geomx-online-user-manual/Content/NGS_DND/Running_DND.htm#Running3
13. Limma,R package for differential gene expression analysis for NanoString GeoMx and heart snRNA-seq data, version 3.44.3;http://bioconductor.org/packages/release/bioc/html/limma.html
14. edgeR, R package for differential gene expression analysis for NanoString GeoMx data, version 3.28.1 or higher;https://bioconductor.org/packages/release/bioc/html/edgeR.html
15. EnhancedVolcano, R package for generating volcano plots for differential genes for analysis on NanoString GeoMx data, version1.6.0; https://bioconductor.org/packages/release/bioc/html/EnhancedVolcano.html
16. fgsea, R package for gene set enrichment analysis on NanoString GeoMx and heart snRNA-seq data, version 1.14.0; http://bioconductor.org/packages/release/bioc/html/fgsea.html
18. Viral-ngs, a collection of pipelines for viral genomic analyses including genome assembly and metagenomic classification, version 2.0.21; https://viral-ngs.readthedocs.io/en/latest/; https://dockstore.org/organizations/BroadInstitute/collections/pgs
19. Scikit-learn, Python module for machine learning, version 0.23; https://scikit-learn.org/stable/
20. Statsmodels, Python module for statistical modeling version 0.12.1 https://www.statsmodels.org/stable/index.html
21. ldsc, Python module for GWAS heritability analysis. https://github.com/bulik/ldsc
22. MAGMA, C++ command line interface for gene-level GWAS analysis version 1.08b
https://ctg.cncr.nl/software/magma
23. scCODA, statistical testing for compositional analysis for scRNA-seq data , v0.1.1.post1, https://github.com/theislab/scCODA/releases/tag/0.1.1.post1
24. adjusted_rand_score from sklearn.metrics.cluster was used to compute rand index for sub-clustering. https://scikit-learn.org/stable/modules/generated/sklearn.metrics.adjusted_rand_score.html
25. DecontX, ambient RNA removal from scRNA-seq count matrix data (part of the "celda" package) https://github.com/campbio/celda version 1.5.11
26. GSVA,R package for gene set enrichment analysis was used to estimate the ssGSEA score for the alveoli NanoString GeoMX data. https://www.bioconductor.org/packages/release/bioc/html/GSVA.html
27. Seurat R package for snRNA-seq data analysis v3.2.1
28. R packages ggplot2 v3.3.2, dplyr 0.8.0.1, reshape2 v1.4.3 and cowplot v1.1.0 for visualization
29. liger R package v0.5.0 https://github.com/welch-lab/liger (Linked Inference of Genomic Experimental Relationships)
30. RSEM for bulk RNA-seq analysis , v1.2.8. , https://deweylab.github.io/RSEM/
31. STAR for bulk RNA-seq alignment, v2.6.0c , https://github.com/alexdobin/STAR

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Data availability
Processed sequencing data (sc/snRNA-Seq and bulk) are available in the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) under accession no. GSE171668 and raw human sequencing data is available in the controlled access repository DUOS (https://duos.broadinstitute.org/), under Dataset IDs DUOS-000126, DUOS-000127, DUOS-000128 and DUOS-000129. Viral genome assemblies and short-read sequencing data are publicly available on NCBI's Genbank and SRA databases, respectively, under BioProject PRJNA720544. GenBank accessions for SARS-CoV-2 genomes are MW885875-MW885883. Data for other tissues in the biobank will be released as they are acquired.

The processed data is available on the Single Cell Portal:
Lung - https://singlecell.broadinstitute.org/single_cell/study/SCP1052/
Heart - https://singlecell.broadinstitute.org/single_cell/study/SCP1216/
Kidney - https://singlecell.broadinstitute.org/single_cell/study/SCP1214/
Liver - https://singlecell.broadinstitute.org/single_cell/study/SCP1213/

Nanostring GeoMx raw and normalized count matrices are available on GEO under accession no. GSE163530. Raw images will be available upon request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We generated sc/snRNA-Seq atlases of:

Sample size	lung (n=16 donors, k=106,792 cells/nuclei, x=23 specimens; Donors=D1-8, 10-17) heart (n=18, k=40,880, x=19 specimens, D1-8, 10-11,14-17, 27-28, 31-32) liver (n=15, k=47,001, x=16 specimens; D1-7,10-17) kidney (n=16, k= 33,872, x=16 specimens;D4-8,10-12,14-15,17,25-26,28-30) We generated spatial data on the following: lung(n= 17 donors, x= 17 samples, Donors=D8-17,22-24) heart(n=1 donor, x= 1 sample, Donor =D20 heart(n=1 donor, x= 1 sample, Donor =D20) Because these are samples from human COVID-19 autopsy donors, we collected samples from as many donors that would consent over the collection period. We did not perform any power analyses prior to this.
Data exclusions	CellBender was used to remove ambient RNA and other technical artifacts from the count matrices. Following CellBender, individual samples were processed using Cumulus, including filtering out cells/nuclei with fewer than 400 UMI, 200 genes, or greater than 20% of UMIs mapped to mitochondrial genes.
Replication	These are samples from human COVID-19 autopsy donors, so we could not replicate samples
Randomization	These are samples from human COVID-19 autopsy donors, so we could not randomize
Blinding	These are samples from human COVID-19 autopsy donors, so this was not applicable to our study

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Immune Cell Profiling Panel (Core); Nanostring Inc; GMX-PROCONCT-HICP-12, Item 121300101, Lot# 0474026 IO Drug Target Panel; GMX-PROMODNCT-HIODT-12, Item 121300102, Lot# 0474029 Immune Activation Status Panel; Nanostring Inc; GMX-PROMODNCT-HIAS-12, Item 121300103, Lot# 0474032 Immune Cell Typing Panel; Nanostring Inc; GMX-PROMODNCT-HICT-12, Item 121300104, Lot# 0474035 Cell Death Panel; Nanostring Inc; GMX-PROMOD-NCTHCD-12, Lot# 0474050 MAPK Signaling Panel; Nanostring Inc; GMX-PROMOD-NCTHMAPK-12, Lot# 0474047 PI3K/AKT Signaling Panel; Nanostring Inc; GMX-PROMOD-NCTHPI3K-12, Lot# 0474053 Covid-19 GeoMx-formatted Antibody Panel including (TMPRSS2, clone EPR3861; ACE2, clone EPR4436; Cathepsin L/V/K/H, clone EPR8011; DDX5, clone EPR7239; and SARS-CoV-2 spike glycoprotein, polyclonal) ; Abcam; ab273594, Lot# GR3347471-1 GeoMx Solid Tumor TME Morphology Kit; Nanostring Inc; GMX-PRO-MORPH-HST-12; Item 121300310 Alexa Fluor® 647 alpha-Smooth Muscle Actin Antibody, clone 1A4 ; Novus Bio; IC1420R CD68 antibody,KP1 clone from Santa Cruz (sc-20060 AF594)
Validation	Nanostring morphological and staining panels are pre-validated by the manufacturer: https://www.nanostring.com/wp-content/uploads/2020/12/GeoMx_Antibody_Validation_White_Paper-3.pdf Morphological markers were previously demonstrated in human tissue in https://doi.org/10.1101/2020.08.25.267336

Human research participants

Policy information about studies involving human research participants

Population characteristics	Extended Data Table 1 - Patient metadata table
Recruitment	For BWH: Subjects were recruited who had died with positive SARS-CoV-2 NP swab test prior to death, and were consented for autopsy to be performed at BWH less than 24 hours from the time of death. No decisions were influenced by subject age,

race/ethnicity, sex/gender, pre-mortem treatments, or co-morbidities.
For MGH: All patients at the Massachusetts General Hospital (MGH) who succumbed from SARS-CoV-2 infection, as confirmed by the qRT-PCR assays performed on nasopharyngeal swab specimens, were eligible for clinical autopsy upon consent by their healthcare proxy or next of kin. A subset of these patients were also enrolled in the MGH Rapid Autopsy Protocol if they had a history of known or suspected malignancy. Their clinical data and research specimens were collected in accordance with Dana Farber/Harvard Cancer Center Institutional Review Board-approved protocol 13-416.
For BIDMC: The COVID rapid autopsy program was active at BIDMC from April 23, 2020 through May 6, 2020. An email was sent to all physicians caring for COVID patients notifying them about the existence of the program and that participation in the research autopsy program could be offered to families of deceased patients. The decision to offer participation in the autopsy research program to the next of kin of decedents was at the discretion of their treating physicians. In total, five autopsies were performed, representing a small fraction of the patients treated at BIDMC during the initial COVID surge of Spring 2020. No efforts were made to specifically include or exclude subjects based on any demographic data or pre-existing medical condition.
For NYP: Inclusion criteria for autopsies from COVID-19 donors cared for at New York Presbyterian Hospital/Columbia University Medical Center included real-time reverse transcription polymerase chain reaction (RT-PCR) confirmed infection, consent to perform rapid autopsy and post mortem intervals <10 hours. Appropriate consent was obtained from donors or the donors' next of kin. All procedures performed on donor samples were in accordance with the ethical standards of the IRB and the Helsinki Declaration and its later amendments. Frozen control tissues were assessed by a pulmonary pathologist and represent “uninvolved” regions of biobanked tumor resections. Donor characteristics reflect the age, gender, and race representation of patients admitted to New York Presbyterian Hospital/Columbia University Medical Center with COVID-19. Control samples were selected to reflect median age distribution of COVID-19 cases included in the study and match the gender distribution.

Ethics oversight

Secondary analysis of samples at the Broad Institute was covered under Massachusetts Institute of Technology (MIT) IRB protocols 1603505962 and 1612793224, or the NHSR (not-involving-human-subjects research) protocol ORSP-3635. No subject recruitment or ascertainment was performed as part of the Broad protocol. Samples added to this protocol also underwent IRB review and approval at the institutions where the samples were originally collected. Specifically, Dana-Farber Cancer Institute approved the protocol 13-416, Partners/Massachusetts General Hospital and Brigham and Women’s Hospital approved the following protocols: 2020P000804, 2020P000849, 2015P002215; Beth Israel Deaconess approved protocol 2020P000406.224. No subject recruitment or ascertainment was performed as part of the Broad protocol. All tissue specimens of lethal COVID-19 and controls collected at New York Presbyterian Hospital/Columbia University Medical Center were under IRB approved protocols (IRB-AAAT0785 and IRB-AAAB2667). Appropriate consent was obtained from patients or the patients' next of kin. All procedures performed on patient samples at New York Presbyterian Hospital/Columbia University Medical Center were in accordance with the ethical standards of the IRB and the Helsinki Declaration and its later amendments.

Note that full information on the approval of the study protocol must also be provided in the manuscript.