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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	Collection of flow cytometry data was performed on the BD FACS Symphony (BD Biosciences) using manufacturer's software.
Data analysis	Flow cytometry data were analyzed using FlowJo V10.6.2 (BD Biosciences). Statistical analysis was performed using JMP Pro v14 (SAS Institute Inc) and GraphPad Prism v8 (GraphPad Software LLC)

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

The data that support the findings of this study are available from the corresponding author upon reasonable request. Sequencing datasets are available on Mendeley.

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	Sample size was not calculated for this study.
Data exclusions	Patients receiving chemotherapy for cancer-related co-morbidities were excluded from the study
Replication	Flow cytometry data were acquired longitudinally using built-in machine calibration allowing for robust comparison of data over time.
Randomization	Patients were categorized based on 30-day survival data from the time of admission to the ICU.
Blinding	Acquisition and data analysis of flow cytometry data were done blindly.

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	Details of antibodies used in the study are summarized in the methods section of the manuscript.
Validation	Each antibody was commercially available and was validated by the manufacturer's.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	ATCC
Authentication	Cell line was authenticated by the manufacturer.
Mycoplasma contamination	Cell lines were negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patients included in the study were intubated, had confirmed SARS-CoV-2+ infection, and met the clinical definition of ARDS

Population characteristics	via Berlin criteria. Control cohort patients were intubated, had confirmed negative SARS-CoV-2, and met the clinical definition of ARDS via Berlin criteria.
Recruitment	Patients were recruited the Medical Intensive Care Unit (MICU) at the University of Alabama Hospital. Control acute lung injury (ALI) tracheal aspirates were obtained at the University of Alabama at Birmingham's and at the Brigham and Women's Hospital (Boston, Massachusetts) from patients presenting with non viral infectious ALI .
Ethics oversight	All data and samples were collected in accordance with the University of Alabama at Birmingham's IRB (COVID Enterprise IRB - IRB 300005127) and with the Brigham and Women's Hospital (Boston, Massachusetts) IRB (IRB-300005209, IRB-2008P000495 and IRB- 2020P000447).

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A
Study protocol	N/A
Data collection	N/A
Outcomes	N/A

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Blood was collected in citrate tubes by venipuncture, cells and plasma were separated by a 400g, 10mins, 4°C centrifugation. The cellular fraction was resuspended in PBS-EDTA (2.5mM) to match the collection volume and then it was stained for flow cytometry analyses. Tracheal aspirate was collected by instillation of three separate 10-ml aliquots into endotracheal tube via 14 Fr in-line suction catheter and sample is aspirated back between each aliquot. Collected aspirate is then mechanically dissociated on ice using 18G needle and syringe. Airway immune cells were recovered after an 800g, 10 minutes, 4°C centrifugation, washed with PBS-EDTA (2.5mM) and stained for flow cytometry.
Instrument	BD FACS Symphony
Software	Collection of flow cytometry data was performed on the BD FACS Symphony (BD Biosciences) using manufacturer's software. Flow cytometry data were analyzed using FlowJo V10.6.2 (BD Biosciences).
Cell population abundance	No cells were sorted. Cell percentages are reported in figure S2.
Gating strategy	Gating strategy is shown in Figure S1.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.