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Reporting Summary

Nature Portfolio 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 Portfolio 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 clinical data collection. Flow cytometry data was collected using FlowJo v10.8.0
Data analysis	R with Rstudio was used for data analysis, including the cytofkit2 package. ClustVis was used for Principle Components Analysis. No custom code was used.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Access to data in this study will be controlled to respect privacy of study participants. Data will be made available on request to the corresponding author.

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	No samples size calculation was made prior to enrollment. This was a convenience sample of all Omicron cases admitted to NCID, Singapore, from 1-18 Dec 2021, when public health measures for containment of Omicron in Singapore mandated all individuals with suspected Omicron infection were admitted to NCID.
Data exclusions	No data excluded after individuals meeting study eligibility criteria were identified, except as described in the age-matching process (Supp Figure 1). From an eligible cohort of 101 Omicron variant infection, 87 were age-matched with 87 out of 287 Delta variant infections.
Replication	The SARS-CoV-2 RBD-specific memory B cell ELISpot and Spike protein flow cytometry-based assay (SFB assay) for antibody detection were performed in duplicate. Given limited cell availability, replication was not performed for whole blood immunophenotyping or identification of SARS-CoV-2-specific T cells by Intracellular Cytokine Staining
Randomization	No randomization performed
Blinding	No blinding performed

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	Flow cytometry antibodies for whole blood immunophenotyping and Intracellular Cytokine Staining (ICS) is described in Supplementary Table 1 and 2 respectively
Validation	The specificity of the antibodies were validated by cell treatment followed by flow cytometry, to ensure that the antibody binds to the antigen stated by manufacturer; the validation reports are available at manufacturer's website. The dilutions used in this study were validated in house on healthy donor blood samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Data collected was age, sex, comorbidity index (per Charlson score), ethnicity, known prior infection (either from serological or virological (PCR/antigen) testing as appropriate), COVID-19 vaccination history
Recruitment	This was a convenience sample of all Omicron cases admitted to NCID, Singapore, from 1-18 Dec 2021, when public health measures for containment of Omicron in Singapore mandated all individuals with suspected Omicron infection were admitted to NCID. This was age-matched with a Delta cohort
Ethics oversight	Waiver of informed consent for collection of clinical data from individuals infected with the Omicron variant was granted by

Ethics oversight	the Ministry of Health (MOH), Singapore, under the Infectious Diseases Act as part of the COVID-19 outbreak investigation. Retrospective data collection from individuals with Delta infection was approved by the institutional ethics committee (REF: 2020/01122). Written informed consent was obtained from study participants for collection of biological samples after review (REF DSRB: 2012/00917).

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	Study has not been registered
Study protocol	No trial protocol has been published, as this was an observational study conducted during under emergency conditions (Omicron outbreak)
Data collection	Recruitment was 1-18 Dec 2021 for Omicron variant infections and 27 April-11 August 2021 for Delta variant infections. All study participants were recruited during admission to the National Centre for Infectious Diseases (NCID), Singapore. Immunologic analysis was performed at A*Star ID Labs, Singapore and SARS-CoV-2 culture at the National University of Singapore.
Outcomes	Primary clinical outcome of interest is the proportion of individuals developing radiologic pneumonia. We also examined the rate of severe infections, which we defined as development of hypoxia requiring supplemental oxygen. These are standard measures used in the literature and by public health bodies to categorise COVID-19 severity.

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 samples were obtained in cell preparation tubes (CPT) from individuals enrolled at NCID. Twenty five µL of whole blood was stained with antibodies as stated in Supplementary Table 1 for 20min in the dark at room temperature (RT) and followed by lysis of erythrocytes with 1mL of 1.2X BD FACS Lysing solution (BD cat#349202) for 10min at RT. 300µL of PBS was added after the incubation and centrifugated at 800 x g for 5min. Samples were then washed with 1mL of PBS and transferred to polystyrene FACS tubes containing 5 ?L (2.4 x 103 beads) of CountBright Absolute Counting Beads (Invitrogen Cat#C36950, Lot 2324193).
Instrument	Cells were acquired with the CytekTM Aurora cytometer running SpectroFlo® Version 2.2.0.3 with automated unmixing
Software	Cells were analyzed using FlowJo v10.8.0.
Cell population abundance	Cell counts were calculated using counting beads as indicated in the methods.
Gating strategy	Gating strategies for whole blood immunophenotyping and intracellular staining are presented in Supplementary Figures 4, 5 and 6.

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