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Corresponding author(s): Galit Alter
Lael M Yonker

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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	ForeCyt® Standard Edition 8.1 was used to collect Luminex, ADNP, ADCP and ADCD assay. Glycan Acquisition Software Version 3500 V1.0.3 was used to collect glycan traces Tecan-i-control V.3.4.2 was used to collect ELISA data.
Data analysis	Microsoft Excel 365 was used to compile experimental data and patient information. Violin plots and statistical analysis was performed with GraphPad Prism v.8.4.2. Flower plots were generated in RStudio (v.1.3 and R v.4.0) using 'ggplot2' package (v.3.3). GlycanAssure Data Analysis software v.1.1 was used to analyze glycan traces. PCA in 'stats' package (4.0.3) was used to reduce the multivariate features into independent components and the number of components representing more than 90% of variances were then used for Umap visualization. Umap implemented in 'umap' package (0.2.7.0) was used to map the multivariate features into two dimension with the parameter (neighbor = 10, min.dist = 0.1) and then the mapped data were visualized using 'ggplot2' package (v.3.3). The integrated functions in 'systemRology' package(https://github.com/LoosC/systemsseRology) (1.0) were used to perform feature selection and partial least-squares discriminant analysis(PLS-DA) implemented in 'ropls' package (1.22.0). Spearman correlation coefficients were calculated using 'rcorr' function in 'Hmisc' package (4.4.2) and the p values were corrected by 'Benjamini-Hochberg' correction implemented in 'stats' package (4.0.3). The correlation networks were properly lay-outed and visualized using 'ggraph' (2.0.4) and 'igraph' (1.2.6) package with later manual adjustment using Adobe Illustrator (2020).

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

All relevant data are included in this manuscript. Source data are provided with this paper.

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 sample size calculation was performed. We included all pediatric COVID-19 or MIS-C patients treated at Massachusetts General Hospital between March and June 2020 who gave informed consent. Adult patients were selected based on the pediatric sample size. Based on experiences from previous studies, sample sizes are assumed to be sufficient.
Data exclusions	SARS-CoV-2 seronegative samples were excluded from the multivariate analyses and univariate analyses of ADCD, ADCP and ADNP. Samples were defined sero-positive when they had detectable titer (by Luminex) for IgG1, IgM and/or IgA1 and a negative cut-off was defined as the average value negative plasma samples plus 5 times the standard deviation. For multivariate analysis, the feature, whose proportion across samples was less than 65% compared with the value of PBS control, was excluded. This exclusion-criteria was pre-established.
Replication	All experiments were run in duplicates and Luminex and functional assays (ADCD, ADNP and ADCD) repeated for most of the samples. Results between repeats were comparable.
Randomization	Samples were randomly distributed in 96 well plates
Blinding	Investigators were blinded during data collection. Group allocation had to be revealed to perform the data analysis.

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

1 .Mouse Anti-Human IgG1-PE (Southern-Biotech, #9054-09, clone:HP6001)
2. Mouse Anti-Human IgG2-PE (Southern-Biotech, #9060-09, clone:31-7-4)
3. Mouse Anti-Human IgG3-PE (Southern-Biotech, #9210-09, clone:HP6050)
4. Mouse Anti-Human IgG4-PE (Southern-Biotech, #9200-09, clone:HP6025)
5. Mouse Anti-Human IgM-PE (Southern-Biotech, #9020-09, clone:SA-DA4)
6. Mouse Anti-Human IgA1-PE (Southern-Biotech, #9130-09, clone: B3506B4)
7. Mouse Anti-Human IgA2-PE (Southern-Biotech, #9140-09, clone: A9604D2)

8. anti-human CD11b BV605 (BD, #562721, Clone ICRF44)
9. Anti-guinea pig complement C3 goat IgG fraction (MP Biomedical, #855385. polyclonal)
10. anti-human CD66b Pacific Blue (Biolegend, #305112 ,clone G10F5)
11. anti-human IgG-Fc-HRP (Bethyl Labs, #A80-148P, polyclonal)
12. anti-human IgM-Fc-HRP (Bethyl Labs, #A80-100P, polyclonal)
13. anti-human IgA-Fc-HRP (Bethyl Labs, #A80-102P, polyclonal)
14. anti-human IgG-Fc (Bethyl Labs, #A80-148A, polyclonal)
15. anti-human IgM-Fc (Bethyl Labs, #A80-100, polyclonal)
16. anti-human IgA-Fc (Bethyl Labs, #A80-102, polyclonal)

Validation

All antibodies are well established and quality controlled by the manufacturer. Additional information and references can be obtained on the company websites.
The use of antibodies 1-4 was previously validated: Brown EP, Licht AF, Dugast AS, Choi I, Bailey-Kellogg C, Alter G, et al. High-throughput, multiplexed IgG subclassing of antigen-specific antibodies from clinical samples. J Immunol Methods. 2012;386(1-2):117-23.
Antibody 9 was described here: Fischinger, S., J. K. Fallon, A. R. Michell, T. Broge, T. J. Suscovich, H. Streeck, and G. Alter. 2019. 'A high-throughput, bead-based, antigen-specific assay to assess the ability of antibodies to induce complement activation', J Immunol Methods, 473: 112630.
Antibody 10: Karsten, C. B., N. Mehta, S. A. Shin, T. J. Diefenbach, M. D. Slein, W. Karpinski, E. B. Irvine, T. Broge, T. J. Suscovich, and G. Alter. 2019. 'A versatile high-throughput assay to characterize antibody-mediated neutrophil phagocytosis', J Immunol Methods, 471: 46-56.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

HL60 cells (promyeloblast)
THP-1 cells (human acute monocytic leukemia)

Authentication

None of the cell lines used were authenticated.

Mycoplasma contamination

Cell lines were not tested for mycoplasma contamination

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics

We analyzed 25 children/young adults (ages 0-20 years, median = 15y) and 34 adults ages 22-76 years, median = 33.5y, 52% female) diagnosed with mild disease, and 26 hospitalized adults (age between 30-79, 53% female) with severe SARS-CoV-2 infection. Additionally, 17 children/young-adults (0 -22 years, median 3.5y, 17% female) diagnosed with MIS-C and 18 SARS-CoV-2 convalescent adults (ages: 27-58y, median: 33y, 55% female)

Recruitment

Patients visited the respiratory illness clinic (RIC) or were hospitalized at a MassGeneralBrigham site in Massachusetts, USA. There was no bias in the patient recruitment.

Ethics oversight

The study was approved by the MassGeneralBrigham IRB. Study number #2020P000955, #2020P000804 and #2020P000849.

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

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

ADNP
After phagocytosis incubation HL-60 cells were pelleted and surface stained with anti-CD11b OR primary neutrophils were stained with anti-CD66b. Cells were washed with PBS and fixed with 4% para-formaldehyde. Cells were washed with PBS after fixation, resuspended in PBS and stored at 4C protected from light for up to 24h, if flow cytometric analysis was not immediately possible.

	ADCP THP-1 cells were pelleted and fixed with 4% para-formaldehyde and washed with PBS after fixation. Cells were then resuspended in PBS and stored at 4C protected from light for up to 24h, if immediate flow cytometric analysis was not immediately possible.
Instrument	IntelliCyt® iQue Screener PLUS
Software	ForeCyt® Standard Edition 8.1 was used to collect and analyze the data.
Cell population abundance	Differentiated HL-60 neutrophils were identified by CD11b surface expression. Usually >90% of single cells were CD11b positive. Primary neutrophils were identified by CD66b surface expression. CD66b expression was donor dependent bu usually >95% within the single cell gate. All single cells were considered THP-1 cells.
Gating strategy	All events were gated for granulocutes using FSC-H and SSC-H and single cells subsequently selected using SSC-A and SSC-H. For ADNP assay: HL-60 differentiated neutrophils were selected by CD11b positivity or primary neutrophils selected for CD66b expression. Phagocytic cells identified in the BL4-H channel. Phagocytic THP-1 cells were directly determined in the single cell population.

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