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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 Authors & Referees 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<br>*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<br>*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 | Excel |
| Data analysis | Prism, Igor, R, Excel , SAS, MATLAB |

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/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 main data supporting the results in this study are available within the paper and its Supplementary Information. All data generated in this study, including source data and the data used to make the figures, are available in Mendeley data with the identifier http://dx.doi.org/10.17632/2f73pzdkr4.1.

# 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

# Life sciences study design

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

| | |
|---|---|
| Sample size | Three sets of data were used:<br>1) Discovery cohort (only in SI): 81 samples from 60 patients (21 samples had 2 time points).<br>2) Model-building cohort: 472 samples (386 people, some of whom had multiple time points).<br>3) Model-testing cohort: 300 samples (300 people, each sampled once). |
| Data exclusions | 1 data point from the model-building cohort was excluded from the model because it was not measured by the instrument due to a mechanical failure (only 1/12 of assays had a missing value that it did not allow for modelling). Additionally, the immunocompromised patients were not included in modelling. |
| Replication | We 'replicate' our results by using a second blinded cohort and achieving similar sensitivity and specificity. |
| Randomization | Not relevant. |
| Blinding | We were blinded to all samples run in the third cohort until after we built the models on the second cohort. |

# 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 |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☒ | ☐ Clinical data |

## Methods

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

## Antibodies

| | |
|---|---|
| Antibodies used | Anti His Tag antibody: ThermoFisher MA121315BTI<br>Anti Human IgG antibody: Bethyl Labratories A80-148B<br>Anti Human IgM antibody: Thermo Fisher MII0401<br>Anti Human IgM antibody: Abcam ab214003<br>Human anti SARS-CoV-2 Spike antibody: Creative Biolabs CR3022<br>Human anti SARS-CoV-2 Spike antibody: Creative Biolabs CBFYR-0119<br>Human anti SARS-CoV-2 Spike antibody: Creative Biolabs CBFYR-0120 |
| Validation | Validated with spike and recovery as well as dilution linearity experiments. Data for these experiments are provided in the Supplementary information. |

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | Cohort 1: 81 plasma samples from Massachusetts General Hospital (MGH) in Boston, MA, USA were used. This sample cohort consisted of three groups: (1) patient plasma collected before the COVID-19 outbreak; (2) plasma collected during the pandemic from patients presenting with symptoms of SARS-CoV-2 at the Emergency Department (ED) with a negative NP RNA test; and (3) serial plasma samples collected during the pandemic from patients who had tested positive for SARS-CoV-2 infection and were hospitalized for COVID-19.<br><br>Cohort 2: 472 samples consisting of (1) plasma samples collected prior to October 1, 2019 from healthy adults with no recorded respiratory infection in their medical history at the time of collection (100 individuals); (2) adults with a recorded respiratory infection within the two-month period prior to sample collection, collected before October 1, 2019 (100 individuals; this group included individuals who had bacterial pneumonia (12 individuals), pneumonia unspecified (10 individuals), upper respiratory infection (URI) unspecified (50 individuals), and viral pneumonia or other viral infection (28 individuals); (3) adults who tested positive for SARS-CoV-2 by NP RT-PCR (172 samples from 91 individuals taken at multiple timepoints); (4) adults who tested negative on NP RT-PCR for SARS-CoV-2 (100 samples from 95 individuals taken at multiple timepoints). |

| | |
|---|---|
| | Cohort 3: 300 additional samples. 68 of which were from adults who tested positive for SARS-CoV-2 using NP RT-PCR within the last 5–34 days. The remaining 232 samples were pre-pandemic controls, all collected before October 1, 2019, and which included (1) 20 patients with bacterial pneumonia in the past 31 days; (2) 20 patients with unspecified pneumonia in the past 31 days; (3) 50 patients with URI within the past 31 days; (4) 42 patients with a confirmed viral respiratory illness within the past 31 days; and (5) 100 healthy individuals with no recorded respiratory viruses in their medical history. |
| Recruitment | Patients who came for a clinical purpose were asked whether leftover blood from their clinical labs could be used for research. |
| Ethics oversight | All samples were collected under approval of the Institutional Review Board for Human Subjects Research at Partners Healthcare. |

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