

## 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 n/a for this study

Data analysis n/a for this study

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](#)

Data is available from the corresponding author upon reasonable request.

## Field-specific reporting

# Life sciences study design

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

Sample size	For the COVID-19 group, sample size was based upon 1) availability of autopsy brain tissue of hospitalized subjects with positive RT-PCR testing for SARS-CoV-2 and 2) quality of brain tissues. 24 patients were selected based upon these criteria. For the control group, 10 age-matched subjects with comparable medical conditions were selected.
Data exclusions	Immunoperoxidase staining was not performed on one subject of the COVID-19 group (#15) due to issues with tissue processing during antigen retrieval; however, routine gross and histopathological examination through haematoxylin&eosin staining was performed. Concerning the quantification of activated microglia, estimation of cell density was not performed two subjects (#20-#21) at the level of the medulla due to incomplete sectioning of the brainstem upon autopsy. In-situ hybridization and immunogold TEM was also performed for some of the IHC+ samples, but results were not satisfactory due to prolonged fixation in formalin and paraffin embedding of the specimens (data not shown).
Replication	Immunoperoxidase staining procedures were repeated at least three times to ensure reaction consistency. All reported immunoperoxidase staining data was replicated by two independent histotechnologists blind to clinical data.
Randomization	Not relevant for this study, due to involvement of human autopsy tissue.
Blinding	Histopathological evaluation was performed by three independent morphologists and neuropathologists blind to patient clinical data. Disagreements were resolved by consensus. Morphometrical analyses (quantification of reactive microglia) was performed blind to both subject group and patient clinical data.

## 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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

### Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Antibodies

Antibodies used	Immunohistochemistry Antibodies: CD3 Antibody (Polyclonal Rabbit Anti-Human, Dako Omnis, Code Number: GA503); CD20 Antibody (Monoclonal Mouse Anti-Human, Clone KP1, Dako Omnis, Code Number: M0814); CD61 Antibody (Monoclonal Mouse Anti-Human, Clone Y2/51, Dako Omnis, Code Number: M0753); CD68 Antibody (Monoclonal Mouse Anti-Human, Clone L26, Dako Omnis, Code Number: M0756); HLA-DR Antibody (Monoclonal Rabbit Anti-Human, Clone: LN-3, Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA); GFAP Antibody (Polyclonal Rabbit Anti-Human, DAKO Omnis, Code Number: GA524); SARS-CoV-2 Nucleocapsid Protein Antibody (Rabbit Anti-Human, Sino Biologicals, 40143-R001); SARS-CoV-2 Spike Subunit 1 Antibody (Monoclonal Rabbit Anti-Human, Clone 007, Sino Biological, Code Number: 40150-R007); ACE2 Receptor Protein Antibody (Rabbit Anti-Human Polyclonal, Abcam, Code Number: ab15348); TMPRSS-2 Protein Antibody (Rabbit Anti-Human Monoclonal, Abcam, Code Number: ab242384).
Validation	SARS-CoV-2 Nucleocapsid and Spike Subunit 1 Antibodies were validated through SARS-CoV-2 infected Vero E6 cells and autopsy-derived lung tissue from SARS-CoV-2 infected patients as positive controls. Non-infected cells and lung sections deriving from autopsy cases predating COVID-19 pandemic were used as negative controls (data shown in Supplementary Figure 1).

# Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	<p>Twenty-four (24) COVID-19 patients were included in the study (11 females, 13 males). The mean age of the included subjects was 73±13.7 years. Available clinical information, hospitalization time, neurological findings, ante-mortem head CT findings and autoptic findings were reported in table 1.</p> <p>Ten (10) age-matched control subjects were included in the study (2 female, 8 male). The mean age of included controls was 74±14 years. Available clinical information and autoptic findings were reported in table 2.</p>
Recruitment	<p>Not applicable for this type of study. Sample size was based upon 1) availability of autopsy brain tissue and 2) adequate quality of brain tissues.</p>
Ethics oversight	<p>All procedures were carried out in accordance to the Declaration of Helsinki. Samples were anonymous to the investigators and used in accordance with the directives of the Committee of the Ministers of EuropeanUnion member states on the use of samples of human origin for research.</p>

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