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The extent of neuroradiological findings in COVID-19 shows correlation with blood biomarkers, Glasgow coma scale score and days in intensive care

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ABSTRACT

Background and purpose: A wide range of neuroradiological findings has been reported in patients with coronavirus disease 2019 (COVID-19), ranging from subcortical white matter changes to infarcts, haemorrhages and focal contrast media enhancement. These have been descriptively but inconsistently reported and correlations with clinical findings and biomarkers have been difficult to extract from the literature. The purpose of this study was to quantify the extents of neuroradiological findings in a cohort of patients with COVID-19 and neurological symptoms, and to investigate correlations with clinical findings, duration of intensive care and biomarkers in blood.

Material and methods: Patients with positive SARS-CoV-2 and at least one new-onset neurological symptom were included from April until July 2020. Nineteen patients were examined regarding clinical symptoms, biomarkers in blood and MRI of the brain. In order to quantify the MRI findings, a semi-quantitative neuroradiological severity scale was constructed a priori, and applied to the MR images by two specialists in neuroradiology.

Results and conclusions: The score from the severity scale correlated significantly with blood biomarkers of CNS injury (glial fibrillary acidic protein, total-tau, ubiquitin carboxyl-terminal hydrolase L1) and inflammation (C-reactive protein), Glasgow Coma Scale score, and the number of days spent in intensive care. The underlying radiological assessments had inter-rater agreements of 90.5%/86% (for assessments with 2/3 alternatives). Total intraclass correlation was 0.80.

Abbreviations: ADEM, acute disseminating encephalomyelitis; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GCS, Glasgow Coma Scale; GFAp, glial fibrillary acidic protein; ICU, intensive care unit; IL-6, interleukin-6; Nerases, neuroradiological severity scale; NfL, neurofilament light chain; NIH, national institute of health; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SWI, susceptibility weighted imaging; t-tau, total tau; UCHL1, ubiquitin carboxy-terminal hydrolase L1

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Previously reported neuroradiological findings in COVID-19 have been diverse and heterogenous. In this study, the extent of findings in MRI examination of the brain, quantified using a structured report, shows correlation with relevant biomarkers.

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Introduction

The Coronavirus disease 2019 (COVID-19) causes a wide spectrum of symptoms and clinical manifestations, ranging from asymptomatic to critical illness and death. A range of neurological deficits has been described in COVID-19 patients, including infarcts, suspected autoimmune reactions, cognitive and psychiatric symptoms, and decreased consciousness.[1,2] Several publications and case reports have described neuroimaging findings in patients with COVID-19 and neurological complications.[3–10] The imaging findings are heterogenous and diverse and encompass both negative scans, focal findings such as infarcts, necrotizing encephalopathy, encephalitis and regional contrast enhancements,[3–6] as well as general findings including widespread white matter changes and numerous microbleeds and/or microthromboses.[5,11,12] So far, the findings have been descriptively reported with the prevalence of each finding usually given as a percentage of the examined population. Imaging patterns have been described, but not homogenously or consistently between studies.[4–6] Thus, a general overview of common or typical imaging findings related to COVID-19 and correlations between imaging findings and other biomarkers has been difficult to extract from the literature. A novel specific visual score for signs of vascular pathology in CT scans was associated with an increased risk of mortality in COVID-19 patients.[13]

Neurological manifestations of COVID-19 may represent individual combinations of direct effects of viral infection, para-infectious or post-infectious inflammation, and complications from prolonged intensive care.[14–16] Biomarkers of CNS injury, such as neurofilament light chain protein (NfL, a marker of axonal injury), and glial fibrillary acidic protein (GFAp, a marker of astrocytic injury), are reported to be increased in patients with COVID-19 in both plasma and CSF.[17,18] The rationale for using these blood biomarkers in COVID-19 has recently been reviewed specifically.[19] Blood biomarkers associated with CNS injury provide additional information regarding different injury processes and thus have the potential of improving medical management of patients with COVID-19.[17,19,20]

A handful of articles describing group-level correlations between blood biomarkers and neuroimaging findings in COVID-19 have been published. Rapalino et al. describes two groups of patients with COVID-19.[21] One group (n = 7) had a distinct pattern of leukoencephalopathy, which was associated with obesity, acute renal failure, mild hypernatremia and anaemia. Tuma et al. report a cohort of 55 COVID-19 patients where 43 had encephalopathy and 39 underwent neuroimaging (9 of them brain MRI).[22] Imaging findings were described as "mostly non-specific". IL-6 in CSF was analysed in six patients and within normal range in three. Paterson et al. showed increased levels of NfL in blood and CSF of patients with COVID-19 and neurological presentation.[23] Strong correlations were shown for NfL levels and imaging signs of encephalitis or acute disseminating encephalomyelitis (ADEM). Other biomarkers of neuronal damage, such as GFAp and UCHL1, have not been extensively reported in the setting of COVID-19.

Neither severity of respiratory symptoms nor neurological status correlate consistently with neuroradiological findings, and associations between clinically available biomarkers and neuroradiological findings are not sufficiently described. An elucidated association between the extent of neuroradiological findings and biomarkers would add to our understanding about the pathophysiology in general and the neuroinvasive properties of the virus in particular. Associations to neurological symptoms such as level of consciousness and to duration of hospitalization in an intensive care unit (ICU) would facilitate clinical assessment.

The purpose of this study was to quantify the extent of neuroradiological findings using an MRI-based structured report and severity scale relevant for patients with COVID-19, and to investigate correlations between these scores with clinical findings, duration of intensive care and biomarkers in blood from patients with COVID-19 and neurological symptoms.

Material and methods

Patients and study design

This was a prospective single-centre study. Nineteen patients with positive PCR for SARS-CoV-2 in nasopharyngeal swabs (Abbott, Abbott Park, IL, USA) and at least one new-onset neurological symptom were included from April until July 2020. Pathological neurological findings were documented as follows: cranial nerve affection, central or peripheral paralysis, extrapyramidal, sensory symptoms and altered mental status including confusion, encephalopathy and reduced level of consciousness graded using the Glasgow Coma Scale (GCS). The most severe neurological symptoms including GCS score during the hospitalization were documented, as well as current symptoms and GCS score within 48 h before MRI. Time between debut of COVID-related symptoms and MRI as well as the number of days in ICU were recorded.

Nineteen patients were included and investigated with MRI of the brain. The National Institute of Health (NIH) criteria for COVID-19 severity grading were used to classify patients as mild (1), moderate (2), severe (3) or critical (4).[24] As a measure of respiratory status, the lowest PaO_2/FiO_2 ratio at any time was documented for patients treated in intensive care. All patients were treated with low molecular weight heparin daily, in weight-dependant dosage (5/10/15,000 IU) during hospitalization.

The study was approved by the Swedish Ethical Review Authority (2020–01883). A subset of patients with new-onset neurological symptoms was selected from a larger prospective observational study with ethical approval (2020–01623). Since the patients included in the present study was gathered from two prospective cohorts, they have also been described in previous studies and case reports from the same research group.[25–28] Those studies had different aims and none of them focused on radiological findings. The Declaration of Helsinki and its revisions were followed. Written informed consent was obtained from each patient, or next-of-kin if a patient was unable to give consent.

Biochemical analysis

Plasma analysis

Routine blood work-up was collected upon admission and thereafter (on a daily basis for patients in ICU), with analyses made of C-reactive protein (CRP), ferritin, fibrin D-dimer and interleukine-6 (IL-6). The results of blood sample analysis were retrospectively scrutinized to identify both the highest recorded values and the values closest in time to MRI. For each blood biomarker, the highest

recorded value during hospitalization was defined as the maximum value ("max"). Any results retrieved within 48 h of MRI were noted as "<48h". Both values were used independently in subsequent analyses.

CNS injury biomarker analysis

The CNS injury biomarkers GFAp, NfL, t-tau and ubiquitin carboxy-terminal hydrolase L1 (UCHL1) in plasma were analysed at the Clinical Neurochemistry Laboratory of the Sahlgrenska University Hospital. Measurements were performed using a 4-plex Single molecule array (Simoa) assay on an HD-X analyzer (Human Neurology 4-Plex A assay, N4PA Advantage Kit, 102,153), as previously described.[17] Intra-assay coefficients of variation were < 8% for all analytes. The CNS injury biomarkers (GFAp, NfL, T-tau and UCHL1) were taken within 48 h of MRI in nine patients and within 3–7 days in five patients (total median 2 days). The remaining five patients did not have CNS injury biomarkers retrieved close enough in time to MRI and were not included in this particular analysis.

Neuroradiological assessment

MRI. All patients were examined with MRI of the brain upon clinical request. The exact protocol, including injection of contrast media, was individually determined based on clinical circumstances. Sixteen patients underwent the COVID-19-intended routine protocol and 10 of these included contrast media. The remaining three patients had slightly shorter protocols, but all of them included T2-weighted TSE images and/or FLAIR, susceptibility-weighted imaging (SWI-sequence), and diffusion weighted imaging. Fifteen patients were examined at 3 Tesla (Philips Achieva dStream, Best, the Netherlands) and four at 1.5 Tesla (Siemens Avanto fit, Erlangen, Germany).

Neuroradiological structured report and severity scale (Nerases). A novel structured report was created for the specific purpose of quantifying the extent of findings associated with COVID-19. The report was constructed a priori – prior to evaluation of the included patients – and based on the existing observational studies on neuroradiological findings in COVID-19 available at the time of study design.[2–6] These five studies collectively describe 197 brain MRIs of COVID-19 patients (13+73+27+47+37). Based on the reported findings of these 197 examinations from the literature, a structured report was constructed, containing 16 multiple choice items. The report was designed with the intention of covering all but the most uncommon of the findings described in the available literature.

Each item was assessed with either yes/no (5 items), a three-step interval (1 item), or yes/no/undecisive (10 items), where the "undecisive" alternative was intended for assessments of contrast enhancement when no injection was made, and for images with severe artefacts. A points system was added to this, allocating 0–3 points per item. This step was also performed a priori to the evaluation of the included patients, based only on information from available literature. The points system was constructed to separate findings with low expected specificity and non-convincing association with COVID-19, from findings with high specificity, clinical importance and stronger association with COVID-19:

- 1 point was allocated to findings of low specificity and improbable clinical significance, but possible association with COVID-19, in effect punctate SWI abnormalities and unspecific white matter changes.
- 2 points were allocated to types of findings with possible or probable clinical impact and plausible association with COVID-19, such as punctate infarcts, extensive SWI abnormalities and contrast enhancement patterns (when available).
- 3 points was allocated to acute findings that have strong association with COVID-19, such as venous thromboses, territorial infarcts and haemorrhage.

After the a priori version of the scale was constructed, a specialist in neuroradiology (DF; blinded to most clinical and all laboratory data) assessed and scored all patients with the severity scale twice, with a 4-week interval, allowing for assessment of intra-rater agreement. A second specialist in neuroradiology (JW) separately scored all patients, allowing for assessment of inter-rater agreement. Three patients were reassessed (still blinded) following a disambiguation in the instruction. At a subsequent occasion, a consensus scoring between the radiologists was achieved, which was used thereafter.

During data processing, the scale was slightly adjusted a posteriori, omitting the items "increased signal in olfactory nerve" and "prominent perioptical spaces", which both had less than 70% inter-rater agreement and weaker support in the literature. No other fitting of the model to the data was performed, so the content and structure of the scale was not in any way based on the specific patients included in the present study.

The final scale, referred to below as the Neuroradiological severity scale (Nerases), is presented together with user instructions in Table 1. Points from all items are added up to a sum called 'Nerases score', and the point range of the final scale was 0–26 or 0–32, without or with contrast media.

Patients with 0–2 total points were classified as 'MRI-negative', whereas having 3+ points was considered 'MRI-positive'. The rationale behind this dichotomization was that unspecific findings such as white matter changes and solitary microbleeds can generate one or two points (MRI negative), whereas three or more points can only be reached by having multiple or more distinctive findings (MRI positive).

Statistics

Intra- and inter-rater agreement was evaluated using Cohen's kappa, separately for items with two and three alternatives. Agreement of the total score was analysed using the intra-class correlation coefficient. Correlations between levels of biomarkers and radiological severity were calculated using Spearman's rank correlation. Based on previous literature, a hypothesis for positive correlations was used (with the exception of GCS scores, for which negative correlation was anticipated). Clinical findings were compared to Nerases score using the Mann-Whitney U test, with a hypothesis of higher Nerases in the presence of positive findings. Statistical calculations were performed using SPSS and Jamovi (an open-source R interface, version 2020, Meddecide package).

Results

Nineteen patients were included and scored. The demographics, comorbidities, biomarker results and MRI findings of the included patients are summarized in Table 2 A-D. The number of days from symptom debut to MRI and days spent in ICU are also noted in the table. With the exception of confusion, the worst recorded neurological symptoms were identical to the symptoms present <48 h of MRI for all patients, indicating that the timepoint of brain MRI was adequate.

The extent of neuroradiological findings in terms of Nerases score ranged from 0 to 19, with a median of 4. Seven patients were categorized as MRI-negative with Nerases scores of 0–2; the remaining 12 were MRI-positive. Representative sample images are shown in Fig. 1.

The intra-rater agreement of the adjusted scale was 91.6% for dichotomous items, yielding a kappa value of 0.684, at a 15.75% rate of positive findings. For items with three alternatives, agreement was

Table 1
The neuroradiological severity scale (Nerases). Scores (0–3) for each item are presented in the four columns to the right. One lesion can yield points for several different items. Previously known and old lesions were disregarded. Item 2 refers to an intraparenchymal bleeding that is larger than "punctate" – which refers to a rounded delineated finding of a few millimetres. Punctate abnormalities on susceptibility-weighted images (SWI) can yield either 1 or 2 points depending on the number of lesions (item 3), and an additional 2 points if at least one abnormality is ovoid-shaped or in a COVID-associated location – namely corpus callosum or juxtacortical (item 4). Territorial infarcts are classified as item 6, but can also fulfil other item criteria. Increased white matter signal in T2/ FLAIR images count as white matter lesions, even if they are contiguous with cortical lesions. CC = corpus callosum; DWI = diffusion-weighted imaging; MCP = medial cerebellar peduncle. Pathological contrast enhancement is assessed when available, increasing the range of the scale from 026 to 0–32.

Score Category	Item	Parameter	0	1	2	3
Bleeds	1	Subarachnoid haemorrhage	No			Yes
	2	Parenchymal bleed > punctate	No			Yes
	3	No. of punctate SWI-abnormalities…	No	1–4	5+	
	4	…with ovoid shape / in CC or juxtacortical	No		Yes	
Infarcts and focal lesions	5	Bilateral focal thalamic lesions	No			Yes
	6	Other focal lesions (e.g., infarcts > punctate)	No			Yes
	7	Punctate infarcts / DWI abnormalities	No		Yes	
	8	Venous thrombosis	No			Yes
White matter changes	9	In deep white matter (incl. unspecific)	No	Yes		
	10	In CC / MCP / juxtacortical white matter	No		Yes	
	11	In brain stem or medial temporal lobe	No		Yes	
Contrast enhancement	12	In parenchyma / cranial nerves	No/NA		Yes	
	13	In meninges	No/NA		Yes	
	14	In white matter lesions	No/NA		Yes	

92.4% and kappa 0.859. Inter-rater agreement for individual items was 90.5%/86%, yielding kappa values of 0.59/0.74. The total Nerases score had an intraclass correlation of 0.80 (95% CI: 0.55–0.92, $p < 0.001$).

Significant correlations with Nerases score were found for GFAp, total tau and UCHL1, as well as for CRP taken within 48 h of MRI, number of days in ICU, and GCS score. These are shown with rho and p values in Fig. 2. Correlation coefficients were also calculated for all other included biomarkers (NfL, CRP, ferritin, fibrin, IL-6, PaO_2/FiO_2 ratio, NIH score and age). Ferritin <48 h and fibrin <48 h were near-significant, with rho values of 0.401/0.390 and p values of 0.078/0.075, respectively. None of the other markers were significant, with rho values ranging from 0.095 to 0.320 and p values ranging from 0.700 to 0.091.

As regards the dichotomization between MRI-positive and -negative patients, the MRI-positive patients had significantly higher values of GFAp and t-tau and significantly lower GCS scores. These are shown as box plots with p values in Fig. 3.

Dichotomous clinical findings, including presence of neurological symptoms, were compared to Nerases score using Mann-Whitney U-tests. Patients with moderate or severe brain injury (defined as GCS score ≤12 and ≤8 respectively) within 48 h from MRI had significantly higher Nerases scores compared with patients with higher GCS scores ($p = 0.032$ / 0.007). No statistical differences in Nerases score were found for cranial nerve affection, central or peripheral paralysis, sensory symptoms or confusion, or any of the listed comorbidities.

Discussion

Reported neuroradiological findings in COVID-19 have been diverse, with unclear correlations with clinical and laboratory findings. This study quantifies the extent of brain MRI findings in a cohort of patients with COVID-19 and neurological symptoms using a structured report and severity scale constructed specifically for this purpose. The resulting score showed a strong correlation with levels of GFAp and total tau in plasma, which are biomarkers for CNS damage. Correlations were also found for UCHL1, number of days in ICU, GCS score and CRP taken within 48 h of MRI.

Previous publications of COVID-19 have reported and summarized neuroradiological findings in frequencies, tables and a number of described patterns,[2–6] but with slightly differing terminology and classifications, rendering direct comparisons difficult. Correlations between imaging findings and other parameters, such as biomarkers and symptoms, have been largely cumbersome to extract from the literature. The semi-quantitative severity score in this article (Nerases) was created with the intention to facilitate such comparisons.

Previous publications have shown that the level of NfL in CSF is associated with COVID-19 severity and neurological symptoms[18] and that NfL in plasma is increased in cases with severe COVID-19.[17] The recent publication by Paterson et al. showed increased levels of NfL but not GFAp in blood and CSF in patients with COVID-19 and neurological presentation, especially those with encephalitis and encephalomyelitis.[23] In the present study, NfL was the only biomarker of CNS damage that did not correlate with extent of neuroradiological findings. Although the present study had a different design, this result differs from the findings of Paterson et al. It may be explained to some extent by the fact that most blood samples were collected within 48 h from MRI, while NfL peaks within 2–3 weeks from the injury, causing possible mismatch.[29] Other possible explanations may include differences in patient cohorts.

Nerases did not correlate with focal neurological symptoms, but did correlate with level of consciousness. This is in line with previous reports that patients with COVID-19 and severe neurological symptoms often have normal neuroimaging.[30] The present study corroborates the relationship between biomarkers of CNS damage in COVID-19 and changes on brain MRI. The correlation with GCS score and duration of ICU stay implies some degree of clinical validity. Future studies can evaluate how neuroradiological findings can be used to differentiate COVID-19 from other diseases, from effects of long-term ICU care, and possibly for prognostication.

The main limitation of the study is the small sample size. Not all patients had the exact same set of investigations performed due to the clinical situation. Furthermore, patients were included at different timepoints along the disease trajectory, which may have affected the results. Since the examinations were requested based on clinical indication (symptoms), the risk of too early imaging was considered very low. Since all included MRI findings persist for days or weeks, the risk of too late scanning was also considered low. Also, a graphical comparison of the IL-6 results and time point of MRI showed a considerable match (data not shown).

Another limitation was that the timing of the blood samples could have been optimized to match the time profile for each biomarker to symptom onset and time of MRI. This was not logistically possible during the current study, but could have improved the validity of the results. Longitudinal samples of biomarkers with time profiles and rates of change could give further information. The MRI scans used

Table 2
A–D. A): Descriptive features and biomarker results. B): Number of patients (%) with comorbidity. C): Number of patients (%) with each neurological symptom, within 48 h of MRI and at worst timepoint. D): Number of patients (%) with each imaging finding described in the Nerases scale. Abbreviations: SWI, susceptibility-weighted imaging; CC, corpus callosum; MCP, medial cerebellar peduncle; MTL, medial temporal lobe; CE, contrast enhancement; WMC, white matter change; WML, white matter lesion. Units are mg/L for CRP and fibrin, ug/L for ferritin, and ng/L for IL-6, GFAp, NfL, t-Tau and UCHL1.

A) Descriptives	n	Median	Minimum	Maximum	B) Comorbidity	n (%)
Age in years (13 male, 6 female)	19	62.0	34.0	76.0	Diabetes mellitus	7 (37)
Nerases score	19	4	0	19	Obesity	9 (47)
GFAp	14	221	36.5	63,861	Hypertension	10 (53)
NfL	14	141	15.0	877	Smoking	1 (5)
t-tau	14	1.91	0.340	10.4	Cardiac disease	4 (21)
UCHL1	14	47.0	9.70	1163	Chronic lung disease	3 (16)
CRP <48h	16	63.0	5.60	259	Immunosuppression	2 (11)
CRP max	19	342	77	517		
Ferritin <48h	14	1113	103	7274		
Ferritin max	19	1894	155	32,785	D) Prevalence of Nerases items	n (%)
Fibrin <48h	15	2.40	0.400	9.40	1. Subarachnoid haemorrhage	1 (5)
Fibrin max	19	4.80	0.600	93.1	2. Parenchymal haemorrhage	1 (5)
IL-6 <48h	15	39.0	6.00	424	3. Punctate SWI abnormalities. . .	9 (47)
IL-6 max	19	174	29.0	2746	4. . . .with special shape or location	8 (42)
GCS <48h	19	9	3	15	5. Bilateral thalamic lesions	1 (5)
GCS worst	19	8	3	15	6. Other focal lesions	3 (16)
NIH score	19	4	2	4	7. Punctate infarcts	2 (11)
PaO_2/FiO_2 ratio	17	78.0	46.5	341	8. Venous thrombus	0 (0)
Days in ICU	19	16	0	42	9. White matter change (WMC)	18 (95)
Days, symptom debut to MRI	19	23	4	51	10. WMC in CC/MCP/juxtacortical	4 (21)
					12. CE in parenchyma	2 (11)
C) Neurological symptoms	<48 h/MRI	Max/worst			13. CE in meninges	0 (0)
Cranial nerves	8 (42)	8 (42)			14. CE in WML	2 (11)
Central motor	9 (47)	9 (47)				
Peripheral motor	11 (58)	11 (58)				
Extrapyramidal	0 (0)	0 (0)				
Coordination	2 (11)	2 (11)				
Sensory	5 (26)	5 (26)				
Confusion	12 (63)	18 (95)				

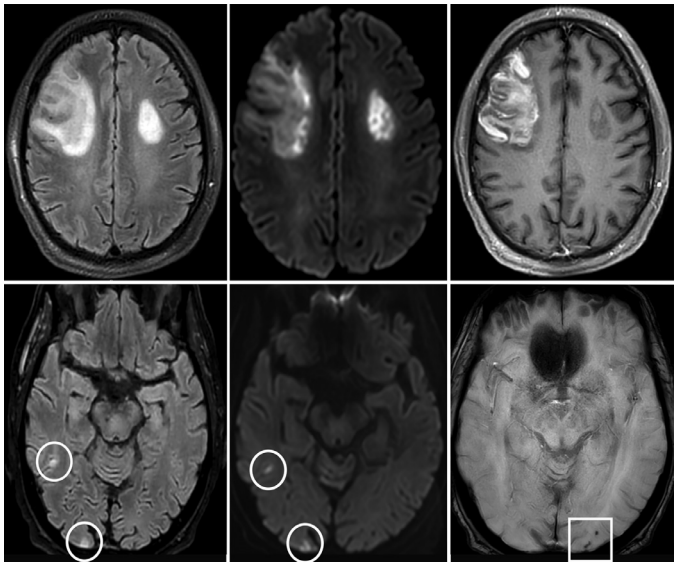

Fig. 1. Two patients with representative findings.

The top row shows images from a 49-year-old male patient, with (from left to right) FLAIR, DWI (b = 1000) and T1 post gadolinium. The images show bilateral frontal subacute infarcts with contrast enhancement. The left infarct is limited to deep white matter, a finding previously described in COVID-19. The patient scores on the Nerases scale for focal lesion (item 6, 3 points), white matter change in deep white matter (item 9, 1 point), contrast enhancement in parenchyma (item 12, 2 points) and enhancement in white matter lesion (item 14, 2 points), for a total of 8 points.

The bottom row shows images from a 74-year-old male patient, with (from left to right) FLAIR, DWI (b = 1000) and SWI. The images show patchy cortical infarcts (circles), a small subarachnoid haemorrhage and a parenchymal microbleed in white matter (both in square). The patient scores on the Nerases scale for subarachnoid (item 1, 3 points) and punctate (item 3, 1 point) bleedings, with atypical form (item 4, 2 points, not shown), punctate infarcts (item 7, 2 points) and white matter changes in both deep white matter, corpus callosum and brain stem (items 9–11, 1 + 2 + 2 points, not shown), for a total of 13 points.

were clinically initiated and not all examinations used a COVID-dedicated protocol. However, none of the imaging features assessed in this study was considered to be highly sensitive to specific sequence related differences, and SWI was consistently used for the assessment of microbleeds. For these reasons, the differences in protocol were not considered to have substantial impact on the results, and the structured report was in fact intended to be applicable to most standard MRI protocols.

The severity scale used in this study is a de novo constructed scale based on qualitative information from previous literature and applied to a clinical material. The selection of radiological findings included as items in the scale and the allocation of points was based on a limited amount of published data available at the time of study design (197 relevant patients). As our understanding of neuro-COVID gradually increases, the selection and score allocation in the rating scale may be reconsidered before further use. At a first glance, the cut-off level to MRI-positive at 3 points may appear arbitrary. The scale contains several elements that are unspecific in nature when regarded individually, such as punctate WMC or micro bleeds. On the other hand, those findings may also be directly related to COVID-19 pathology. The construction of a 3-point cut-off means that a few punctate lesions and/or microbleeds are not enough to be considered as a pathological scan, but may add points to the total in conjunction with other findings.

Intra- and inter-rater measurements showed a high percentage of agreement, but moderate kappa values. This mismatch is largely dependant on the unequal distribution of positive findings in each category, with some findings being present in only a few patients. No significant correlations with Nerases could be shown for several of the included markers, including IL-6, or individual neurological symptoms. Insufficient association to the included radiological findings, as well as the low sample size, are plausible explanations for this. The NIH-score (and WHO-score) focuses primarily on level of respiratory symptoms so it is not surprising that there was no

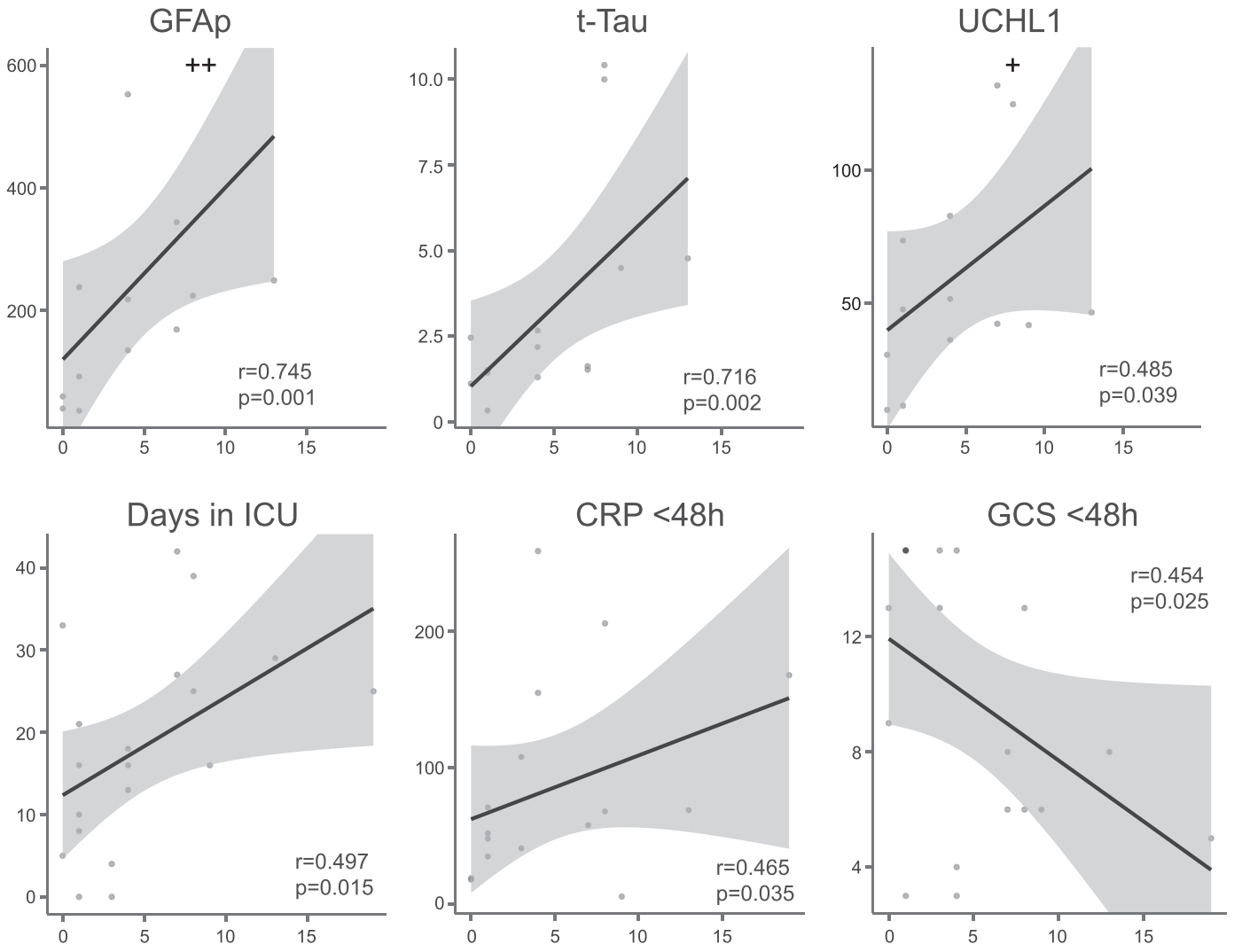

Fig. 2. Spearman correlation coefficients for selected biomarkers (y-axis) compared with Nerases score (x-axis). Extremely high values were truncated for visualization purposes and marked with "+". Units are mg/L for CRP and ng/L for GFAp, t-tau and UCHL1.

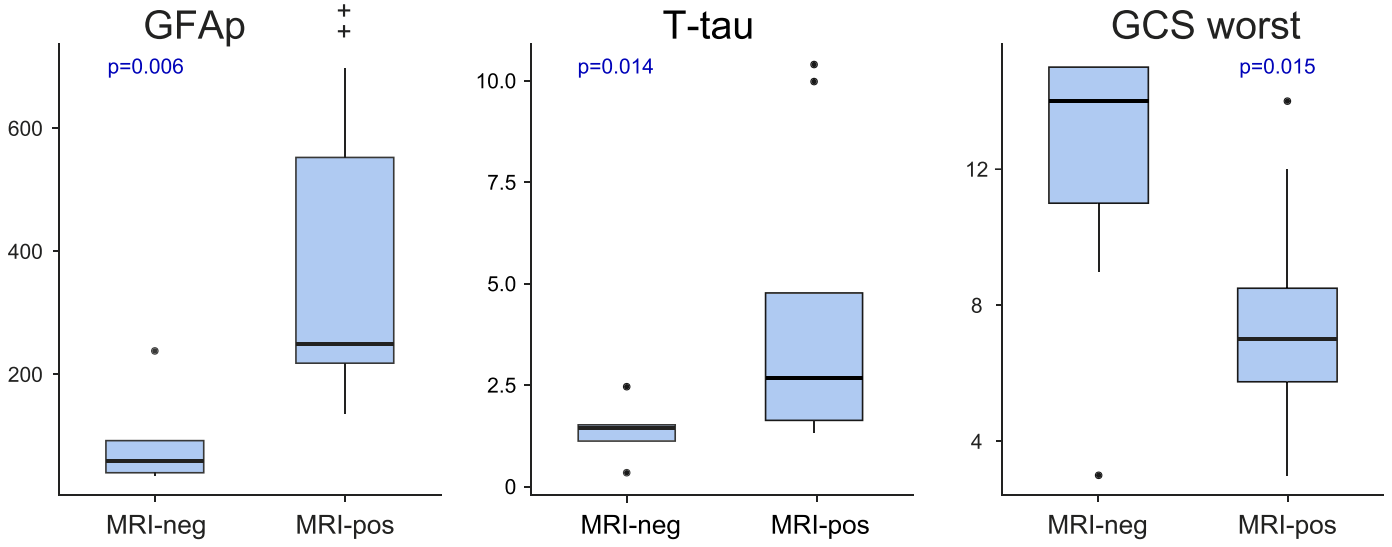

Fig. 3. Boxplots of total tau, GFAp and worst GCS score, comparing MRI-negative (neg) and MRI-positive (pos) patients. All three depicted dichotomizations were significant, with p values shown under each respective title. Two extremely high GFAp values were truncated for visualization purposes, represented with "++".

correlation between this score and the extent of lesions in the brain. Further studies on larger cohorts are needed to explore the relations between specific neurological symptoms and radiological findings. We did not correct for multiple analyses in this study because of the limited sample size and the ensuing risk of introducing a type II error. The presented data is also insufficient for controlling for confounders and for adequately correlating the findings to clinical outcome measures. For example, the "number of days in ICU" is a multifactorial variable and was included in the results mainly as an auxiliary marker of clinical validity. When larger datasets of neuroradiological and neurochemical findings in relation to clinical outcome are available, the scale can be optimized using multivariable modelling and validated to outcome measures such as neurological sequelae.

Due to the diversity and heterogeneity of COVID-19-related neuroradiological findings, correlations with clinical symptoms and other biomarkers have been difficult to assess.

In this study, the extent of brain MRI findings in patients with COVID-19 and impaired consciousness or other neurological symptoms was quantified using a specifically designed structured report and severity scale. The resulting score showed correlation with blood biomarkers for CNS damage, with GCS score, and with number of days in intensive care.

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