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Brain magnetic resonance imaging findings six months after critical COVID-19: A prospective cohort study

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ABSTRACT

Background: COVID-19 patients suffered from neurological symptoms in the acute phase. Whether this led to long-term consequences was unknown. We studied long-term brain MRI findings in ICU-treated COVID-19 patients and compared them with findings in groups with less severe acute disease.

Materials and methods: In this prospective cohort study, 69 ICU-treated, 46 ward-treated, and 46 home-isolated patients, as well as 53 non-COVID-19 controls, underwent brain MRI six months after acute COVID-19. Plasma neurofilament light chain (NfL), a biomarker of neuroaxonal injury, was measured simultaneously.

Results: Ischaemic infarctions existed in 5.8% of ICU-treated patients. Cerebral microbleeds (CMBs) existed in 27 (39.1%) ICU-treated, 13 (28.3%) ward-treated, 8 (17.4%) home-isolated COVID-19 patients, and 12 (22.6%) non-COVID controls. Patients with CMBs were older ($p < 0.001$), had a higher level of plasma NfL ($p = 0.003$), and higher supplementary oxygen days ($p < 0.001$). In multivariable analysis, age (OR 1.06, 95% CI 1.02–1.09) and supplementary oxygen days (OR 1.07, 95% CI 1.02–1.13) were associated with CMBs. The ICU group showed prevalent distribution of CMBs in deep regions.

Conclusion: Age and supplementary oxygen days were independently associated with CMBs; COVID-19 status showed no association. Accumulation of risk factors in the ICU group may explain the higher prevalence of CMBs.

Trial registration: ClinicalTrials.gov NCT04864938, registered February 9, 2021.

Abbreviations: ABNAS, AB Neuropsychological Assessment Schedule; ALT, Alanine aminotransferase; ARDS, Acute respiratory distress syndrome; BMI, Body mass index; CCI, Charlson comorbidity index; CI, Confidence interval; CMB, Cerebral microbleed; COPD, Chronic obstructive pulmonary disease; COVID-19, Coronavirus Disease 19; CRP, C-reactive protein; CSVD, Cerebral small vessel disease; ECMO, extracorporeal membrane oxygenation; FDR, False discovery rate; ICU, Intensive care unit; IMV, Invasive mechanical ventilation; IQR, Interquartile range; LMWH, Low molecular weight heparin; LOS, Length of stay; MARS, Microbleed anatomical rating scale; MFI, Multidimensional fatigue inventory; MRI, Magnetic resonance imaging; NfL, plasma neurofilament light chain; OR, Odds ratio; PaO_2/FiO_2, Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PLT, Platelet count; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SD, Standard Deviation; SWI, Susceptibility weighted imaging; WMH, White matter hyperintensity.

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1. Introduction

Coronavirus disease 2019 (COVID-19) can lead to several acute and long-term neurological complications in the central and peripheral nervous systems [1,2], and some patients, particularly those that were neurologically symptomatic patients in the early phase of the COVID-19 pandemic, showed cerebral microbleeds (CMBs), white matter hyperintensities (WMHs), and strokes, both ischaemic and haemorrhagic [1,3-5].

CMBs, most easily detected on susceptibility-weighted magnetic resonance imaging (MRI) sequences, are small (< 10 mm diameter) hemosiderin deposits formed after blood extravasation from damaged small vessels [6-8]. Once a CMB has occurred, disappearance is unlikely [9-11]. They are associated with an increased risk of ischaemic stroke (odds ratio [OR] 3.59) or intracranial haemorrhage (OR 7.46) [7]. In critically ill patients, CMBs have occurred in conditions like respiratory and cardiovascular failure, influenza requiring venovenous extracorporeal membrane oxygenation (ECMO) treatment [12], disseminated intravascular coagulation [13], sepsis [14], and infective endocarditis [15]. Data on CMBs after critical COVID-19 are insufficient.

WMHs, visible on T2-weighted sequences, are punctate, patchy, or confluent hyperintense areas [6] and are associated with an increased risk of stroke, intracranial haemorrhage, and dementia [16]. Both CMBs and WMHs are part of a pathologic process termed cerebral small vessel disease (CSVD) and have an increasing prevalence with age [6]. Other risk factors for CSVD include arterial hypertension, smoking, diabetes mellitus, hypercholesterolaemia, obstructive sleep apnoea, chronic kidney disease, and branch atheromatous disease, most of which are also among the recognized risk factors for severe or critical COVID-19 [6,17,18]. Plasma neurofilament light chain (NfL) is a biomarker of neuroaxonal injury, recently studied in several neurological diseases [19-21], and the acute phase of COVID-19 [22,23], where higher levels were associated with more severe disease courses and worse outcomes.

Our aim with this prospective cohort study involving controls was to describe brain MRI findings six months after hospital discharge, in ICU-treated COVID-19 patients without major neurological complications and to compare the findings with those in patients treated in a regular ward or isolated at home as well as in non-COVID-19 controls. Furthermore, we aimed to report the factors, including NfL, associated with these findings.

2. Materials and methods

This study is part of the Recovery after critical COVID-19 infection (RECOVID) study project (ClinicalTrials.gov NCT04864938). The study protocol (HUS–1949–2020) was approved by the ethics board of Helsinki University Hospital. All the study subjects gave written informed consent. The study followed the principles of the Declaration of Helsinki. We employed a Strengthening the Reporting of Observational studies in Epidemiology checklist for cohort studies.

2.1. Patients

In our earlier work, we reported in detail the formation of the patient cohort including the inclusion and exclusion criteria [24]. Adult patients diagnosed with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were recruited in Helsinki and Uusimaa Hospital District between March 12 and December 31, 2020. Patients with major neurological diagnoses, developmental disabilities, or substantially impaired hearing or vision were excluded. The level of acute care determined the COVID-19 patient groups (ICU, WARD, and HOME). We also included a CONTROL group with no history of COVID-19. The study subjects were free to choose which parts of the study they participated in. In addition to those previously reported, exclusion criteria included contraindications for MRI (see Electronic supplementary material [ESM]).

2.2. Brain imaging protocol

Brain MRI was to occur approximately six months after hospital discharge or, concerning the home-isolated patients, a positive test result. All imaging was performed with a Philips Ingenia 3 T (Philips Healthcare, Best, the Netherlands) scanner and a 32-channel head coil. The protocol comprised both functional and anatomical imaging. Sequences included resting-state functional MRI, whole brain T1, T2-, and FLAIR-weighted 3D, susceptibility-weighted imaging (SWI), T2 fat saturated and heavily T2-weighted images of the orbit, time-of-flight circle of Willis magnetic resonance angiography, a pseudo-continuous arterial spin labelling, quantitative susceptibility mapping, multi-shell diffusion MRI and intravoxel incoherent motion imaging. A specialist neuroradiologist with >10 years of experience in radiology (J.M.), blinded to clinical details, interpreted the imaging findings. CMBs were counted in SWI sequences and their distribution was documented according to the microbleed anatomical rating scale (MARS) [25]. Infratentorial microbleeds included CMBs in the cerebellum and brainstem, while lobar bleeds included CMBs in the frontal, temporal, parietal, and occipital lobes. WMHs, evaluated in T2 and FLAIR sequences, were categorised according to the Fazekas scale, which records no changes (0), mild (1), moderate (2), or severe (3) changes [26].

2.3. Data collection

We collected data on the hospitalised groups (ICU, WARD) from electronic patient records and ICU data management systems (Apotti, Epic™, Verona, USA; PICIS™, Wakefield, USA; Uranus™, CGI, Montreal, Canada). Data on the HOME and CONTROL groups were collected from the patient records and the study subjects through telephone interviews. We recorded age, sex, comorbidities, body mass index, Charlson comorbidity index (CCI) [27], and admission data including length of hospital and ICU stay, length of supplementary oxygen treatment, need for, and length of invasive mechanical ventilation (IMV), number of proning episodes, anticoagulant dosing (see ESM for more details), and the acute phase laboratory test results (highest alanine aminotransferase [ALT], C-reactive protein [CRP], D-Dimer, ferritin and troponin I values, and lowest platelet count [PLT] during hospital admission). In the HUS Diagnostic Centre, HUSLAB, the reference ranges were plasma ALT for males <50 U/l, for females <35 U/l, C-reactive protein <4 mg/l, platelet count 150 to 360 × 10^9/l, D-Dimer <0.5 mg/l, ferritin for males 20–195 μg/l, for females 15–125 μg/l, and troponin *I* <45 ng/l [28]. We defined the clinical variables in our earlier work [24]. For plasma NfL, we collected samples six months after the acute phase and sent them to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital in Gothenburg, Sweden for analysis with a commercial Quanterix® kit (the Simoa® NF-light assay). The results were compared with in-house-generated normal reference limits for different age groups: 18–50 years <10 pg/ml; 51–60 years <15 pg/ml; 61–70 years <20 pg/ml; over 70 years <35 pg/ml [29]. Study subjects were asked if they were suffering from headache at three months telephone interview, and they answered questionnaires regarding subjective cognitive functioning [AB Neuropsychological Assessment Schedule (ABNAS)] and fatigue [Multidimensional Fatigue Inventory (MFI)] at six months [30,31].

2.4. Statistics

Continuous variables are presented as median and interquartile range (IQR), or mean and standard deviation (SD), while categorical variables are expressed as number of subjects (percentage). In univariable comparisons, we used the chi-squared test or Fisher's exact test for categorical variables. Continuous variables with a non-normal distribution were compared using a non-parametric Kruskal–Wallis test. For multivariable analysis, we used a binomial logistic regression model to compare the factors associated with the presence of CMBs.

Covariables for the multivariable model were selected based on the data (difference between CMB groups in a univariate model) and literature on recognized risk factors (hypertension, hypercholesterolemia, diabetes) [6]. Because multiple tests were conducted, we performed false discovery rate (FDR) correction for multiple comparisons. The FDR-corrected threshold for significance was $p < 0.03$. Analyses were performed with Jamovi project® (version 2.2) and RStudio® (version 1.4.1717).

3. Results

3.1. Patient characteristics

This study comprised 69 ICU-treated, 46 ward-treated and 46 home-isolated COVID-19 patients, and 53 non-COVID controls (Fig. 1). Table 1 summarises demographics, medical history, and clinical admission data in different groups. Forty-five (65.2%) subjects in the ICU group received invasive mechanical ventilation (IMV), and no one received ECMO treatment. ICU patients were older, more often men, and suffered more often from arterial hypertension, hypercholesterolaemia, and diabetes. At the time of recruitment, sequencing of the SARS-CoV-2 variants was uncommon, but as the alpha variant reached Finland only in December 2020 [32,33], and SARS-CoV-2 vaccinations started at the end of December 2020, our study population consisted of unvaccinated COVID-19 cases with the original variant.

3.2. Brain MRI

Study subjects underwent brain MRI at an average of 190 days (SD 29) after the acute phase (approximately six months after hospital discharge, or positive test result for home-isolated subjects). During the acute and follow-up phases of the disease, none of the study subjects had a brain MRI performed or a clinically diagnosed stroke. At six months, three patients in the ICU group had lacunes, one showed signs of old haemorrhagic infarctions in the cerebellum and occipitally (ICU group), and one had a remnant of a haemorrhage in the cerebellum (CONTROL group). Table E1 in the ESM contains all the incidental findings.

3.3. Cerebral microbleeds and white matter hyperintensities

CMBs were found in 48 of 161 (29.8%) COVID-19 patients, in 40 of 115 (34.8%) hospitalised COVID-19 patients, and in 27 of 69 (39.1%) ICU-treated COVID-19 patients. For the prevalence of CMBs (Table 1), the differences between groups were statistically non-significant. The mean number of CMBs was 23.3 (SD 74.0) in the ICU group, 2.7 (SD 2.1) in the WARD group, 1.8 (SD 0.7) in the HOME group, and 1.5 (SD 0.8) in the CONTROL group; no statistically significant differences existed. Two individuals in the ICU group had a very high number of microbleeds (140 and 361) (Fig. 2). Additionally, MRI showed diffuse axonal injury (DAI) in one individual who was excluded from the analyses concerning the number and distribution of CMBs.

COVID-19 patients diagnosed with CMBs, when compared to those without, were older, had more comorbidities, received supplementary oxygen for longer, had longer hospital and ICU length of stay (LOS), and a higher level of plasma NfL at six months (Table 2). For COVID-19 patients, in the multivariable analysis, which included age, supplementary oxygen days, arterial hypertension, hypercholesterolaemia, diabetes, and level of care (ICU, WARD, or HOME), age (OR 1.05, 95% CI 1.01–1.10) and higher number of supplementary oxygen days (OR 1.07, 95% CI 1.02–1.13) had statistically significant associations with the existence of CMBs (Table E2 in the ESM). When the multivariable analysis was repeated for all study subjects, including CONTROLS, only age was significantly associated with the existence of CMBs (OR 1.06, 95% CI 1.02–1.09) (Table E3 in the ESM). All ICU patients received low molecular weight heparin (LMWH); one patient received tinzaparin and everyone else received enoxaparin. When ICU patients with CMBs were compared to those without, no difference in LMWH dosing existed (Table 2).

Fig. 3a shows the mean number of CMBs in different brain regions, grouped according to the MARS scale and excluding the two outliers with hundreds of microbleeds. All the CMBs of the splenium occurred in the ICU group (mean 0.71, SD 1.37, $p = 0.045$); the HOME group showed the highest mean number of CMBs in the brainstem (mean 0.5, SD 0.76, $p = 0.006$). In all groups, CMBs occurred most commonly in the lobar regions (Fig. 3b). The proportion of study subjects with lobar CMBs was

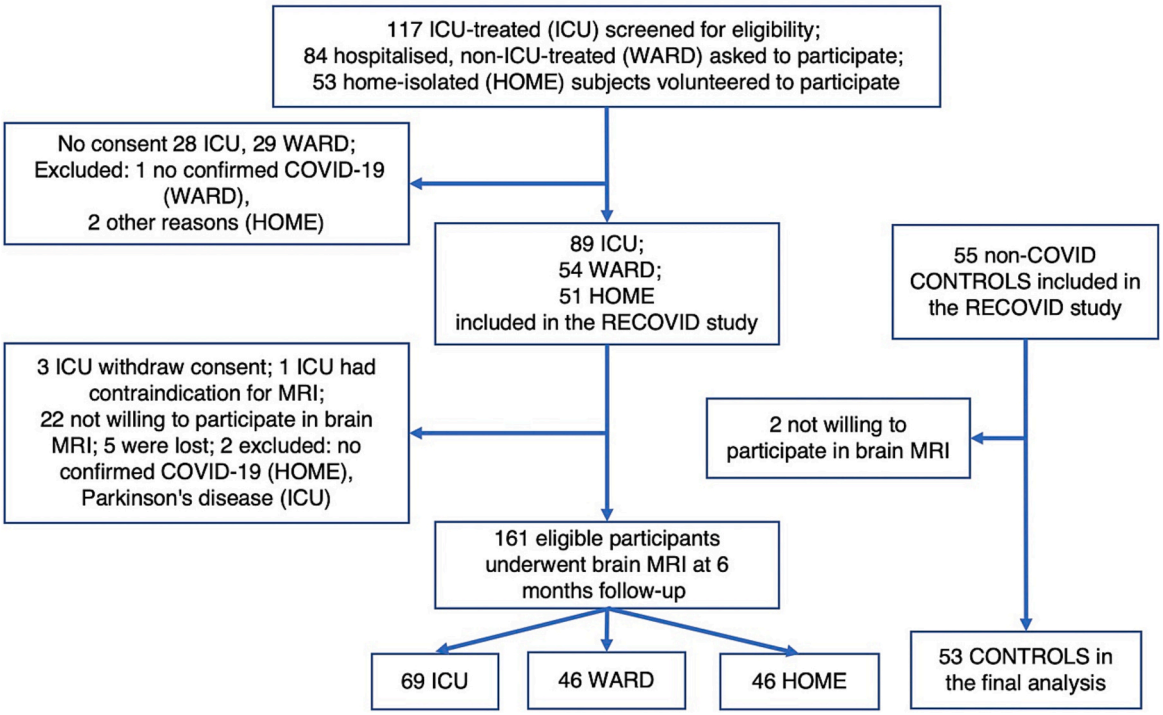

Fig. 1. Flow chart showing the number of study subjects included in the final analysis.

Table 1
Patient characteristics and clinical variables in different severity groups.

	ICU $n = 69$	WARD $n = 46$	HOME $n = 46$	CONTROL $n = 53$	p-Value
Sex, female, n (%)	25 (36.2)	28 (60.9)	33 (71.7)	26 (49.1)	**0.001**
Age, years, median (IQR)	60 (50–66)	57 (49–62)	44.5 (35–52)	55 (49–63)	**< 0.001**
BMI kg/m^2, mean (SD)	30.5 (5.2)[a]	29.0 (4.7)[b]	25.8 (4.1)[c]	–	**< 0.001**
Comorbidities					
Arterial hypertension, n (%)	38 (55.1)	13 (28.3)	8 (17.4)	11 (20.8)	**< 0.001**
Hypercholesterolaemia, n (%)	22 (31.9)	10 (21.7)	4 (8.7)	7 (13.2)	**0.01**
Heart disease, n (%)	11 (15.9)	3 (6.5)	4 (8.7)	1 (1.9)	0.05
Diabetes, n (%)	16 (23.2)	5 (10.9)	2 (4.3)	1 (1.9)	**0.001**
Malignancy, n (%)	5 (7.2)	1 (2.2)	2 (4.3)	1 (1.9)	0.43
Asthma, n (%)	11 (15.9)	12 (26.1)	4 (8.7)	3 (5.7)	**0.02**
COPD, n (%)	0 (0)	2 (4.3)	0 (0)	0 (0)	0.06
Kidney disease, n (%)	3 (4.3)	0	0	0	0.09
Liver disease, n (%)	0	2 (4.3)	1 (2.2)	0	0.19
Psychiatric or neurological comorbidity, n (%)	5 (7.2)	4 (8.7)	1 (2.2)	6 (11.3)	0.38
Admission					
Supplementary oxygen, days, median (IQR)	20 (13.5–24)	5.5 (1–9)	0	–	**< 0.001**
Hospital LOS, days, median (IQR)	20 (15–26)	8 (5–11)	–	–	**< 0.001**
ICU LOS, days, median (IQR)	11 (6–18)	–	–	–	
Received steroid, n (%)	17 (25.4)	–	–	–	
Brain MRI findings					
CMBs detected, n (%)	27 (39.1)	13 (28.3)	8 (17.4)	12 (22.6)	0.06
CMB No. > 3, n (%)	8 (11.8)	4 (8.7)	0	0	0.03 *
CMB No., median (IQR)	2 (1.3–6.8)	2 (1–5)	2 (1–2)	1 (1–2)	0.09
Fazekas 0, n (%)	7 (10.1)	4 (8.7)	15 (32.6)	8 (15.1)	**0.01**
Fazekas 1, n (%)	54 (78.3)	40 (87.0)	28 (60.9)	43 (81.1)	
Fazekas 2 or 3, n (%)	8 (11.6)	2 (4.3)	3 (6.5)	2 (3.8)	

IQR interquartile range, BMI body mass index, COPD chronic obstructive pulmonary disease, LOS length of stay, CMB cerebral microbleed. [a] Data available for 67 of 69 study subjects [b] Data available for 36 of 46 study subjects [c] Data available for 25 of 46 study subjects. Statistically significant p values in bold. * Non-significant after FDR correction.

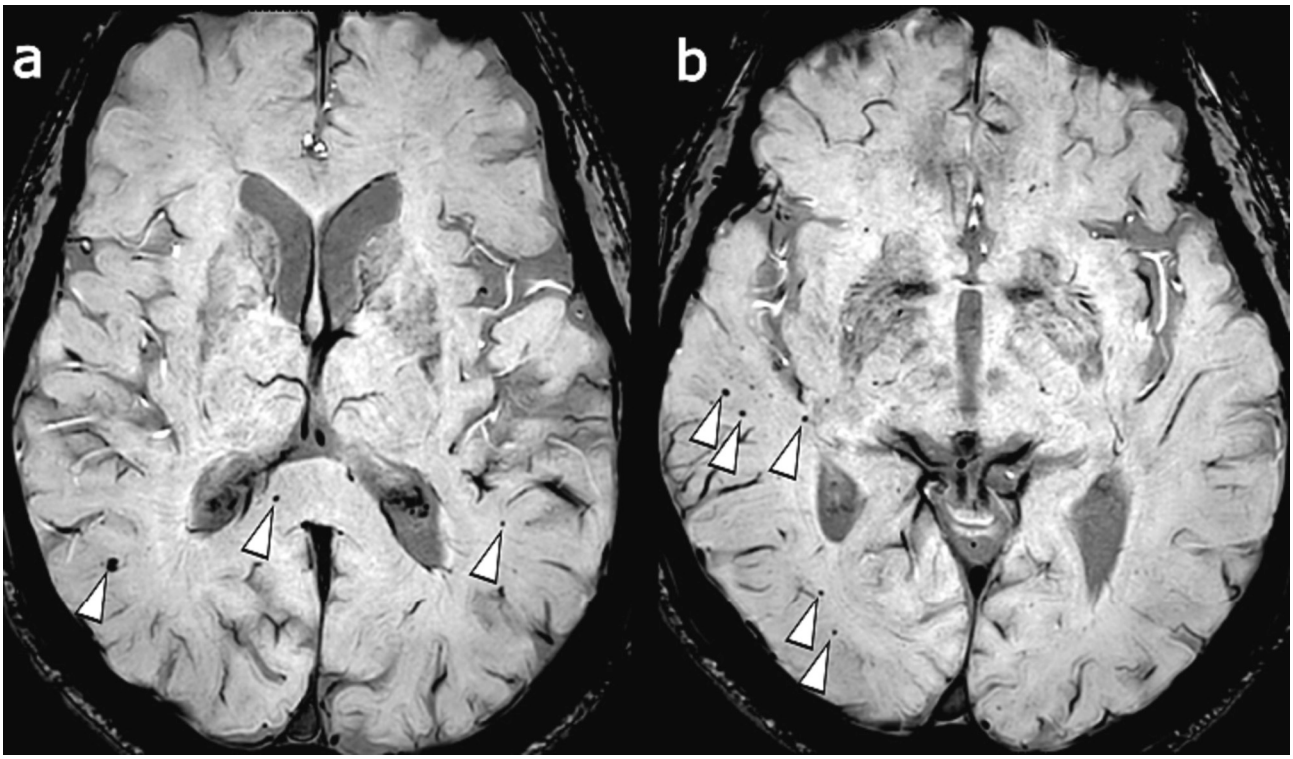

Fig. 2. SWI sequence of brain MRI showing multiple CMBs in an ICU-treated individual with a total of 140 microbleeds. **a** CMBs in the right side of splenium and both temporal lobes **b** CMBs in the right temporo-occipital areas. Some of the CMBs are marked with arrowheads.

the greatest in the ICU group, but the difference was statistically non-significant. In the ICU group, the proportion of patients with deep CMBs was higher than in other groups ($p < 0.001$), because of splenial CMBs (Fig. 3b). In pairwise comparisons, the differences between the ICU and HOME ($p = 0.003$), and ICU and CONTROL groups ($p = 0.001$) were statistically significant.

The Fazekas scale for WMHs in most subjects in all groups (93%) was 0 or 1; in the ICU group, eight patients (11.6%) had a Fazekas scale of 2 or 3 (the differences between groups for Fazekas 2–3 were not statistically significant) (Table 1). COVID-19 patients with a Fazekas scale of 2

Table 2
Characteristics of COVID-19 patients according to the presence of CMBs in brain MRI.

All COVID-19 patients $n = 161$	No CMBs $n =$ 113	CMBs found $n =$ 48	p-Value
Sex, female, n (%)	65 (57.5)	21 (43.8)	0.15
Age, median (IQR)	51 (43–59)	61 (55–67)	< **0.001**
Group ICU, n (%)	42 (37.2)	27 (56.2)	0.04*
WARD, n (%)	33 (29.2)	13 (27.1)	
HOME, n (%)	38 (33.6)	8 (16.7)	
Arterial hypertension, n (%)	35 (31.0)	24 (50)	0.04 *
Heart disease, n (%)	9 (8.0)	9 (18.8)	0.09
Diabetes, n (%)	13 (11.5)	10 (20.8)	0.19
Kidney disease, n (%)	0	3 (6.2)	0.04 *
NfL, pg/ml, median (IQR) [a]	6.6 (4.9–9.1)	9.2 (6.3–15.10)	**0.003**
Suppl. Oxygen, days, median (IQR) [b]	4 (0–15)	13 (3–23)	< **0.001**
ABNAS score, 6 months, median (IQR) [c]	11.5 (5–18.3)	11 (4–19)	0.61
MFI score, 6 months, median (IQR) [c]	54.1 (41–66.3)	51 (33–67)	0.62
Suffering from headache, 3 months, n (%) [d]	25 (24.5)	9 (19.6)	0.51

Hospitalised COVID-19 patients (ICU and WARD) $n = 115$	No CMBs $n =$ 75	CMBs found $n =$ 40	p-Value
CCI, median (IQR) [e]	1 (0–2)	3 (1–3)	**0.002**
Hospital LOS, days, median (IQR)	11 (7.5–19)	20.5 (12.8–30.5)	< **0.001**
Highest ALT, U/l, median (IQR) [f]	72 (39–128)	134 (54–199)	**0.009**
Highest CRP, mg/l, median (IQR) [g]	198 (108–262)	194 (120–299)	0.33
Lowest PLT, x10^9/l, median (IQR) [g]	210 (161–286)	218 (192–262)	0.43
Highest D-dimer, mg/l, median (IQR) [h]	1.1 (0.5–2.2)	1.7 (0.9–4.9)	0.10
Highest ferritin, ug/l, median (IQR) [i]	696 (290–1352)	875 (520–1668)	0.21
Highest troponin I, ng/l, median (IQR) [j]	9 (5–21)	13 (6–56)	0.19

ICU-treated COVID-19 patients $n =$ 69	No CMBs n = 42	CMBs found $n =$ 27	p-Value
ICU LOS, days, median (IQR) [k]	9 (4.3–14)	17 (7.5–29)	**0.006**
IMV, n (%)	25 (59.5)	20 (74.1)	0.33
IMV days, median (IQR) [l]	10 (7–13)	15.5 (12.8–28.3)	**0.002**
IMV days $PaO_2/FiO_2 < 100$ mmHg, median (IQR) [m]	0 (0–3)	1 (1–5)	0.03 *
IMV $PaO_2/FiO_2 < 100$ mmHg, n (%) [m]	11/25 (44)	15/18 (83)	**0.01**
IMV No. of proning episodes, mean (SD) [l]	0.84 (1.07)	1.70 (2.27)	0.10
LMWH dose			
Thrombosis prophylaxis, n (%) [n]	40 (95.2)	21 (84)	0.19
Higher than thrombosis prophylaxis, n (%) [n]	2 (4.8)	4 (16)	
Delirium diagnosis, n (%) [o]	13 (31.7)	11 (44)	**0.01**
SOFA 24 h, median (IQR) [p]	5 (3–7)	7 (3.5–8.5)	0.12

CMB cerebral microbleed, MRI magnetic resonance imaging, IQR interquartile range, NfL neurofilament light chain, ABNAS AB neuropsychological assessment schedule, MFI multidimensional fatigue inventory, CCI Charlson comorbidity index, LOS length of stay, ALT alanine aminotransferase, CRP C-reactive protein, PLT platelet count, IMV invasive mechanical ventilation, PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen, SD standard deviation, LMWH low molecular weight heparin, SOFA sequential organ failure assessment. [a] Data available for 94 of 161 study subjects, measured at 6 months [b] Data available for 159 of 161 study subjects [c] Data available for 137 of 161 study subjects [d] Data available for 148 of 161 study subjects [e] Data available for 114 of 115 study subjects [f] Data available for 111 of 115 study subjects [g] Data available for 112 of 115 study subjects [h] Data available for 98 of 115 study subjects [i] Data available for 70 of 115 study subjects [j] Data available for 93 of 115 study subjects [k] Data available for 69 ICU-treated subjects [l] Data available for 45 IMV treated subjects [m] Data available for 43 of 45 IMV treated subjects [n] Data available for 67 of 69 ICU-treated subjects [o] Data available for 66 of 69 ICU-treated subjects [p] Data available for 57 of 69 ICU-treated subjects. Statistically significant p-values in bold. *Non-significant after FDR-correction.

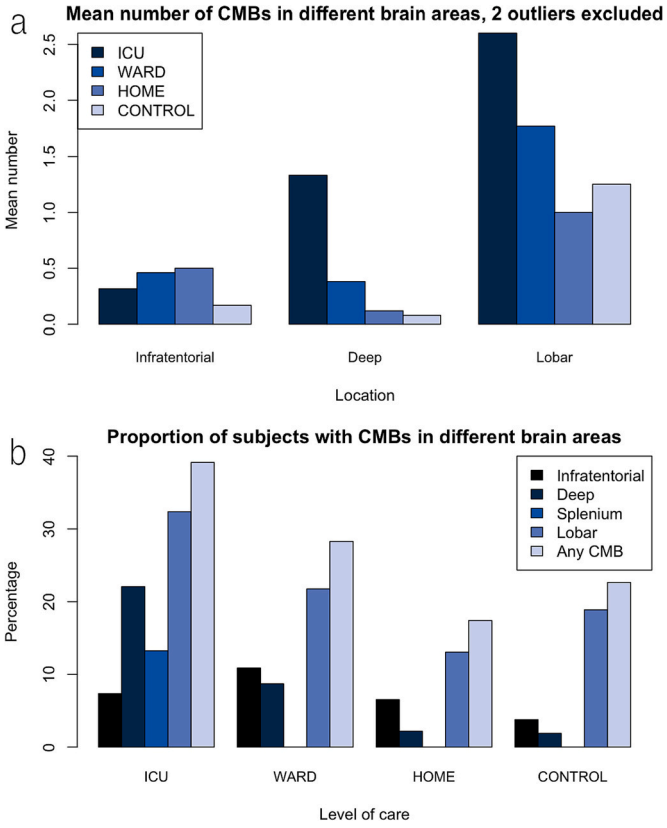

Fig. 3. (a) Mean number of CMBs in different brain areas according to MARS scale (2 outliers excluded) in the three COVID-19 patient groups and the CONTROL group. For deep CMBs, the difference between the groups is statistically non-significant after FDR-correction ($p = 0.046$). (b) Proportion of subjects in the three COVID-19 patient groups and the CONTROL group with CMBs in different brain areas. Data included the 2 outliers. For deep CMBs, the difference in proportion between groups is statistically significant ($p < 0.001$). Splenial CMBs are included in the deep category.

to 3 were older, had greater CCI, suffered more often from arterial hypertension and diabetes, and had a higher plasma NfL level at six months (Table E4 in the ESM).

4. Discussion

In this prospective observational study of six-month follow-up on COVID-19 survivors, we discovered ischaemic infarctions in 6%, CMBs in 39%, and WMHs graded as moderate or severe in 12% of the ICU group. When compared with the WARD, HOME, and CONTROL groups, many of these differences were statistically non-significant and partly explained by confounding factors, such as age and comorbidities. In univariable analyses, factors associated with the presence of CMBs included advancing age, higher CCI, and severity of respiratory failure; COVID-19 status, however, had no association. The distribution of CMBs in the ICU group differed from that in other groups and showed similarities with those previously described after non-COVID-19 critical illness and severe ischaemia with the involvement of deep regions, particularly the splenium of the corpus callosum.

Previous reports of brain MRI findings in COVID-19 patients have

been mainly retrospective and included patients imaged in the acute phase due to clinical symptoms. Our study, with a prospective follow-up of patients not selected for their neurological symptoms and without major neurological comorbidities, provides valuable and more generalisable information about the recovery of COVID-19 survivors. Comparing the findings to a non-COVID control group is a strength; however, the control group represented home-dwelling individuals and we did not include a clinical control group, such as non-COVID ICU-patients with ARDS. Our study has several limitations. Data on the length of comorbidity history (such as hypertension and diabetes) were unavailable. Declines in cerebral vascular health are, however, progressive, and cumulative [9]. In addition, selection and volunteer biases cannot be excluded. No pre-COVID-19 brain imaging was available to study the temporal association between the findings and COVID-19. Plasma NfL, a marker of neuroaxonal injury, was measured only at 6 months' timepoint and not simultaneously with the acute disease process. In a multivariable model, only those covariables that were measured, could be adjusted for. Our data are not sufficient to explore thoroughly the pathophysiological mechanism leading to CMB, but surrogates of inflammation (ferritin, CRP) and thrombosis (LMWH dose, D-dimer) in the acute phase did not differ between patients with or without CMBs. Because our study included the original SARS-CoV-2 variant, the results cannot be fully generalised to infections caused by later variants from 2021 onwards. Finally, we cannot exclude a type 2 error due to the study's moderate sample size.

CMBs can be seen in 3.1–38.3% of the healthy population and their prevalence increases with advancing age [7,10,34]. CMBs, however, are always considered pathological and not part of normal ageing; this association between age and CMBs can probably be partly explained by an age-related increase in vascular health risk and accumulation of risk factors [9]. The prevalence of CMBs in our study was mainly in the same range as previously described, although not all of our patients were previously healthy. However, the HOME group, with a median age of 45 years, had a relatively high prevalence (17.4%) of CMBs when compared to a large general population cohort study that showed a low prevalence (6.5%) of CMBs in the 45–50 year age group [34]. In COVID-19 patients, the prevalence of CMBs has varied between 4% and 52% [35,36]. Diabetics suffer from CMBs more frequently than non-diabetics [37]; this trend existed also in our study but was statistically non-significant. Chronic hypertension is an important risk factor for CMBs, especially in deep and infratentorial locations [7,10,34]. Accordingly, the COVID-19 patients with CMBs in our study had a higher prevalence of hypertension. Our control group, with no history of COVID-19, had a marked (23%) prevalence of CMBs, suggesting the existence of alternative explanatory factors for CMBs other than COVID-19, such as hypertension. Other studies have described an association of CMBs in COVID-19 with acute-phase inflammatory markers, platelets, and more severe kidney and respiratory failure [3,38-40]; in our study, however, both the highest CRP and lowest platelet count were at the same level in patients with and without CMBs, but length of supplementary oxygen treatment, a surrogate of the severity of respiratory failure, was significantly longer in patients diagnosed with CMBs. For unexplained reasons, patients with CMBs had significantly higher ALT levels. Headache, subjective cognitive or fatigue symptoms can be regarded as typical for post-COVID-19 condition [41]; our patients with CMBs did not suffer from those symptoms more than patients with no CMBs.

Pre-pandemic studies of CMBs during and after mechanical ventilation and ARDS have reported that CMBs tend to occur particularly in the juxtacortical white matter and corpus callosum, especially the splenium, but seem to spare the cortex, deep and periventricular white matter, basal ganglia, and thalami [11,42]. These locations resemble those seen in high-altitude sickness which might suggest a common pathogenesis of hypoxaemia [11,42,43]. In 14 critically ill patients suffering from respiratory or cardiovascular failure, CMBs occurred most commonly in the grey and white matter interface, corpus callosum, and cerebellum [44]. Post-ECMO CMBs commonly present in a pattern that involves the splenium of the corpus callosum [45]. The distribution of CMBs in our ICU group resembled the previously described distribution after critical illness, respiratory failure, or ECMO treatment, particularly regarding the splenial CMBs that occurred exclusively in the ICU group. Unlike our study, many previous studies were case series with a limited number of patients and involved individuals imaged because of clinical deterioration in the acute phase [42,44]. A series of four neuropathological COVID-19 cases showed microbleeds at the grey and white matter junction, in the brainstem, deep grey matter structures, and cerebellum; only one case had corpus callosum involvement [46]. CMBs in COVID-19 patients, most of whom were treated in the ICU, occurred most commonly in the juxtacortical white matter and corpus callosum [47-50]. Hypotheses are that microbleeds in COVID-19 may result from hypoxaemia, endothelitis, and vasculopathy [39,46,47,49,51]. In addition, in our study, those in the ICU group diagnosed with CMBs had more severe respiratory failure. Long-term data on COVID-19 findings in brain imaging are scarce and incomparable to ours — two studies have reported changes in white matter microstructure and cerebral blood flow in COVID-19 survivors on follow-up [52,53]. A UK biobank study of brain MRIs pre- and post-COVID-19, when compared to non-COVID-19 controls, showed a greater reduction in grey matter thickness and global brain size [54]. Two out of nine critical COVID-19 survivors with neurological symptoms in the acute phase had innumerable CMBs in a follow-up of more than six months [50].

A large proportion of all study subjects showed WMHs, which were predominantly mild; in 8.6% of the COVID-19 patients, WMHs were classified as moderate or severe. COVID-19 status was not associated with the prevalence of WMHs. In several studies, WMH prevalence in the healthy population has been very variable (5.3 to 100%) and depends on the age group studied [55-59]; in all studies, the prevalence has increased with increasing age, which is in concordance with our findings. In COVID-19, the prevalence of WMHs, in patients aged 51–60 on average, has been 19–20% [60,61]; for WMH volumes in COVID-19 versus non-COVID-19 subjects, the results have been conflicting [53,62]. Several studies have reported nonspecific white matter changes or leukoencephalopathy [1,3,63-65]. Extensive WMH burden has been associated with an increased risk of stroke, ischaemic stroke, intracerebral haemorrhage, Alzheimer's disease, dementia, and death [16].

The number of radiologically detected ischaemic or haemorrhagic strokes in our study population was low. A large cohort study from the Netherlands reported an incidence of clinically relevant ischaemic stroke of 1.8% in hospitalised COVID-19 patients; over 70% had a poor outcome of death or functional dependency at hospital discharge [66]. In critical COVID-19 patients with acute respiratory distress syndrome imaged in the acute phase, 57% had cerebrovascular injury [36]. An explanation for our low number of strokes could be our exclusion of those with a previous history of major neurological comorbidities, or that patients with functional disabilities may have been unwilling to participate in our study. We cannot exclude the possibility that any small ischaemic changes emerging during the acute phase would have been masked by WMH at six months.

At 3–6 months post-COVID-19, 95–100% of survivors have had normal levels of NfL, and no association with neurological symptoms has existed [67-69]. This accords with our results at six months, where the mean NfL concentration was within the normal range, and only 6.5% of the study subjects presented with values above the reference range; those with CMBs or WMHs, however, had higher NfL values than those without CMBs or WMHs. This was also noticeable in the study of Qu and colleagues, where NfL in the nondemented elderly was associated with the presence of CMBs, lacunar infarcts, and moderate to severe WMHs [21].

5. Conclusions

Six months after acute COVID-19, 6% of the ICU-treated patients had mainly lacunar ischaemic infarctions and 39% presented with CMBs. In

the ICU group, the distribution of CMBs resembled that in previously reported cases after critical illness or severe hypoxaemia, with a predilection for the splenium. In a multivariable analysis, age and the length of supplementary oxygen treatment emerged as the only factors independently associated with CMBs; COVID-19 status showed no association. An important next step would be to compare COVID-19 ARDS patients to non-COVID ARDS patients. For all COVID-19 patients, the CMB burden was low.

Ethics approval and consent to participate

The study protocol (HUS–1949–2020) was approved by the ethics board of Helsinki University Hospital. All the study subjects gave written informed consent. The study followed the principles of the Declaration of Helsinki.

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CRediT authorship contribution statement

Henriikka Ollila: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Janne Pihlajamaa:** Formal analysis, Writing – review & editing. **Juha Martola:** Conceptualization, Investigation, Writing – review & editing. **Linda Kuusela:** Investigation, Writing – review & editing. **Kaj Blennow:** Investigation, Writing – review & editing. **Henrik Zetterberg:** Investigation, Writing – review & editing. **Viljami Salmela:** Formal analysis, Writing – review & editing. **Laura Hokkanen:** Formal analysis, Writing – review & editing. **Marjaana Tiainen:** Formal analysis, Investigation, Writing – review & editing. **Johanna Hästbacka:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Declaration of Competing Interest

H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. On behalf of all the other authors, the corresponding author states that there is no conflict of interest.

Availability of data and materials

Consent for public sharing was not included in the original consent formula; within EU/EESC data can be partially shared upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154502.

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