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ORIGINAL ARTICLE

Neurological and (neuro)psychological sequelae in intensive care and general ward COVID-19 survivors

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Abstract

Background and purpose: Coronavirus disease 2019 (COVID-19) affects the brain, leading to long-term complaints. Studies combining brain abnormalities with objective and subjective consequences are lacking. Long-term structural brain abnormalities, neurological and (neuro)psychological consequences in COVID-19 patients admitted to the intensive care unit (ICU) or general ward were investigated. The aim was to create a multidisciplinary view on the impact of severe COVID-19 on functioning and to compare long-term consequences between ICU and general ward patients.

Methods: This multicentre prospective cohort study assessed brain abnormalities (3 T magnetic resonance imaging), cognitive dysfunction (neuropsychological test battery), neurological symptoms, cognitive complaints, emotional distress and wellbeing (self-report questionnaires) in ICU and general ward (non-ICU) survivors.

[†]See Acknowledgement section for all members of the NeNeSCo Study Group.

Results: In al, 101 ICU and 104 non-ICU patients participated 8–10 months post-hospital discharge. Significantly more ICU patients exhibited cerebral microbleeds (61% vs. 32%, $p < 0.001$) and had higher numbers of microbleeds ($p < 0.001$). No group differences were found in cognitive dysfunction, neurological symptoms, cognitive complaints, emotional distress or wellbeing. The number of microbleeds did not predict cognitive dysfunction. In the complete sample, cognitive screening suggested cognitive dysfunction in 41%, and standard neuropsychological testing showed cognitive dysfunction in 12%; 62% reported ≥3 cognitive complaints. Clinically relevant scores of depression, anxiety and post-traumatic stress were found in 15%, 19% and 12%, respectively; 28% experienced insomnia and 51% severe fatigue.

Conclusion: Coronavirus disease 2019 ICU survivors had a higher prevalence for microbleeds but not for cognitive dysfunction compared to general ward survivors. Self-reported symptoms exceeded cognitive dysfunction. Cognitive complaints, neurological symptoms and severe fatigue were frequently reported in both groups, fitting the post-COVID-19 syndrome.

KEYWORDS
affective, brain damage, cognitive, COVID-19, ICU, neurological, neuropsychological, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) primarily leads to respiratory problems but also affects other organs, including the brain [1]. This has been affirmed by imaging studies reporting brain abnormalities, with greater prevalence in more severely ill patients [2]. These brain abnormalities potentially cause cognitive dysfunction, leading to cognitive complaints (e.g., poor concentration), emotional distress (e.g., anxiety, depression, post-traumatic stress), and reduced well-being (e.g., quality of life, social participation) [3]. From a theoretical biological view, the most severely ill patients have the highest risk for brain abnormalities and resulting cognitive dysfunction.

Intensive care unit (ICU) admission, independent of COVID-19, is associated with non-specific structural neuroimaging abnormalities (e.g., lesions, white matter hyperintensities, atrophy) [4]. The pathophysiological mechanisms contributing to these abnormalities (e.g., inflammation, hypoxia, vascular damage) overlap with those proposed to underlie COVID-19 brain abnormalities [4-6]. Therefore, COVID-19 patients admitted to the ICU are expected to have a higher prevalence of brain abnormalities than general ward (non-ICU) patients. Consequently, cognitive dysfunction is primarily expected amongst COVID-19 ICU survivors. A recent systematic review reported significant proportions of patients with cognitive dysfunction in COVID-19 survivors [7]. However, findings regarding the relationship between illness severity and dysfunction are inconsistent and are marked by clinical and methodological heterogeneity [7,8]. Most studies were small, with limited numbers of ICU patients, retrospective, or based on preselected patients with neurological symptoms or cognitive complaints [2,7,8]. Cognitive dysfunction was frequently assessed with screening tools rather than neuropsychological test batteries, potentially overestimating dysfunction [7,8]. Furthermore, brain abnormalities, neuropsychological dysfunction (i.e., cognitive dysfunction and emotional distress), cognitive complaints, and well-being were investigated separately, in distinct samples [2,3,9]. For appropriate follow-up care, knowledge on the complete spectrum of objective and subjective disease consequences is needed.

In the current study different disciplines joined forces to create a more holistic view on COVID-19 consequences. The aim was to investigate whether COVID-19 ICU-admitted patients are more prone to brain abnormalities, neurological and (neuro)psychological consequences than non-ICU patients. The presence, nature, and extent of (1) the neurological sequelae (brain abnormalities and neurological symptoms), (2) the neuropsychological sequelae (cognitive dysfunction and emotional distress) and (3) the subjective illness consequences (cognitive complaints and wellbeing) in ICU and non-ICU patients were compared. It was expected that more pronounced (objective) neurological and neuropsychological dysfunction in ICU than non-ICU patients would be detected. (Subjective) cognitive complaints and wellbeing were expected to be independent of hospitalization, as negative subjective experiences may also occur in the absence of brain damage and cognitive dysfunction [10].

MATERIALS AND METHODS

Study design and participants

A multicentre, prospective cohort study was conducted in six Dutch hospitals (method S1). The protocol was approved by the medical research ethics committee of Maastricht University Medical Centre (NL75102.068.20) and committees of participating centres, pre-registered (ClinicalTrials.gov: NCT04745611) and published [11].

Patients (≥18 years) were eligible if they had been admitted to the ICU or general ward of one of the recruiting hospitals during the first European infection wave (March–June 2020) for treatment of a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Individuals with magnetic resonance imaging (MRI) contra-indications, cognitive impairment prior to hospital admission (based on recorded medical history), physical inability to visit a hospital, or new severe neurological damage after hospital discharge were excluded. Patients were recruited at minimally 6 months post-hospital discharge for (A) a structural 3 T MRI brain scan to assess brain abnormalities, (B) neuropsychological testing to investigate cognitive dysfunction, and (C) to complete questionnaires to examine neurological symptoms, cognitive complaints, emotional distress (anxiety, depression, post-traumatic stress) and wellbeing (quality of life, social participation).

A power calculation with effect size 0.44, grounded in group differences in global cognitive functioning between similar populations (i.e., healthy elderly individuals [12] and a mild stroke cohort [13]), a power of 80% and two-sided α of 0.05, suggested a minimum of 81 participants per group.

Procedures

Recruiting hospitals provided a list of admitted COVID-19 patients. The order of the lists was randomized. Treating physicians checked eligibility and established contact, starting from the top of the list. Inclusion stopped when the intended group size per hospital was reached. Subsequently, patients were informed about the study by the research team and invited for a hospital visit at one of the participating centres. During the visit, an MRI scan and neuropsychological testing were performed. Questionnaires were completed on site or at home on paper or online. Data concerning comorbidity and disease characteristics were extracted from medical files and the CovidPredict database [14]. Data were recorded in the online database, Castor EDC.

Study outcomes

Brain abnormalities

Brain abnormalities were qualitatively evaluated based on a 3 T cranial MRI scan (standardized protocol: T1- and T2-weighted, fluid-attenuated inversion recovery, susceptibility- and diffusion-weighted images). Evaluation was based on a standard neuroimaging assessment repertoire with good interrater reliability [15] (i.e., white matter lesions, cerebral infarcts, lacunes, macrobleeds, microbleeds, perivascular spaces, global cortical atrophy, medial temporal lobe atrophy; see Table S1). The evaluator, a certified neuroradiologist at Maastricht UMC+, was blinded regarding hospitalization and neuropsychological test performance.

Cognitive dysfunction

Global and domain-specific cognitive dysfunction were investigated with a screening tool (Montreal Cognitive Assessment, MoCA) and a neuropsychological test battery consisting of well-known and validated tests with normative data available (Trail Making Test, Stroop, Controlled Oral Word Associations, Category Fluency, Digit Span, Symbol Digit Substitution, Rey's Auditory Verbal Learning Task, Judgement of Line Orientation, and Boston Naming Task). Testing was performed by trained research assistants. The cognitive domains assessed were mental speed and attention, executive function, working memory, memory, visuospatial and language function (Table S2). Performance validity testing was used to screen for suboptimal performance.

Neurological symptoms, cognitive complaints, emotional distress and wellbeing

Commonly experienced neurological symptoms after COVID-19 were scored using a simple questionnaire (method S2). Cognitive complaints, emotional distress (anxiety, depression, post-traumatic stress) and wellbeing (social participation, quality of life, sleep, fatigue) were measured with self-report questionnaires (see Table S3 for the respective constructs and questionnaires).

Statistical analysis

Neuropsychological test scores were corrected for sex, age and education and *z*-score standardized. Cognitive dysfunction was analysed using multivariate analyses comparing each patient's cognitive profile (i.e., pattern of performance on all neuropsychological tests) to normative cognitive profiles, with deviations described in *z*-scores. Multivariate cognitive profile comparisons are based on Huizenga et al. (method S3) [16].

Proportions of dysfunction (*z*-score ≤ −2.0, consistent with a two-sided α of 0.05 [17]) per test and from normative cognitive profiles were computed. For the MoCA, proportions of patients performing below the common cut-off point of 26 were calculated. Analyses were repeated excluding patients suspected of performing suboptimally (score ≤45 on the Test of Memory Malingering, TOMM).

Questionnaire data were mean imputed if ≤15% per patient and questionnaire were missing. Otherwise, the questionnaire was disregarded from analysis. For questionnaires with known cut-off scores, proportions of patients scoring below cut-off were calculated.

Continuous normally distributed variables were presented as mean with standard deviation. Continuous non-normally distributed and categorical variables were presented as median with interquartile range. Non-continuous variables were presented as absolute frequencies and proportions. Group differences were evaluated

TABLE 1 Demographic and clinical characteristics of the ICU and non-ICU COVID-19 group.

Characteristics	ICU ($n = 101$)	Non-ICU ($n = 104$)	p value[a]
Age, years	61.0 [54.0–68.0]	64.0 [53.0–70.0]	0.54
Sex, female	25/101 (25)	37/104 (36)	0.09
Education level[c]			
Low	19/101 (19)	20/104 (19)	0.90
Medium	40/101 (40)	44/104 (42)	
High	42/101 (42)	40/104 (39)	
Premorbid physical functioning, Barthel index	20.0 [20.0–20.0]	20.0 [20.0–20.0]	0.98
Received care after hospital discharge			
Physical therapy	88/101 (87)	59/104 (57)	<0.001
Occupational therapy	45/101 (45)	10/104 (10)	<0.001
Rehabilitation[b]	74/101 (73)	16/104 (16)	<0.001
Psychology	34/101 (34)	15/104 (15)	0.001
Comorbidities			
Chronic cardiac disease	19/91 (21)	19/92 (21)	0.97
Chronic pulmonary disease	9/91 (10)	8/92 (9)	0.78
Chronic kidney disease	5/91 (6)	5/92 (5)	1.00
Malignant neoplasm	2/91 (2)	2/92 (2)	1.00
Diabetes	13/91 (14)	12/92 (13)	0.81
Body mass index, kg/m^2	27.7 [25.1–30.6]	27.1 [25.1–30.8]	0.67
Hypertension	33/91 (36)	28/92 (30)	0.40
Chronic neurological disorder	7/90 (8)	7/92 (8)	0.97
Disease-related parameters			
Length of ICU stay, days	17 (13.0)	–	–
Invasive ventilation, days	14 [8–23]	–	–
Coagulation disorder	20/91 (22)	8/94 (9)	0.01
Delirium	41/87 (47)	4/94 (4)	<0.001
Highest SOFA score	7.0 [5.0–9.0]	–	–
APACHE IV	55.3 (16.7)	–	–

Note: Values are median [interquartile range] or *n*/total *N* (%).

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ICU, intensive care unit; *n*, number of individuals; non-ICU, general ward patients; SOFA, sequential organ failure score.

[a]*p* values are uncorrected and refer to the χ^2 test or Fisher's exact test (where expected cell values were below 5) for dichotomous variables and the Mann–Whitney *U* test for continuous, non-normally distributed or categorical variables.

[b]Includes in-clinic and out-of-clinic rehabilitation.

[c]Education level was separated into low, medium and high based on guidelines of the Dutch Central Bureau of Statistics (Centraal Bureau voor de Statistiek [18]).

with independent samples *t* tests, Mann–Whitney *U* tests, χ^2 tests, or Fisher's exact tests as appropriate. Tests were two-sided with α set at 0.05 and adjusted for multiple comparisons using Benjamini–Hochberg corrections. Reported *p* values are therefore uncorrected but comparisons remaining significant after correction are marked. Analyses were executed using IBM SPSS Version 27 (IBM SPSS Inc.).

After initial analyses, an explorative simple linear regression analysis, assessing the relationship between microbleeds and an average *t* score across all cognitive tests, was added.

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

RESULTS

Demographic and clinical characteristics

Out of 1991 patients admitted to the recruiting hospitals (ICU $n = 428$; non-ICU $n = 1563$), 101 ICU and 104 non-ICU patients were enrolled. 35% of ICU patients and 56% of non-ICU patients were not eligible for participation (Figure 1). This difference in exclusion rate was caused by differences in the lists supplied by the recruiting hospitals. Unlike ICU lists, non-ICU lists included patients who died during their hospital stay, leading to a difference of exclusion

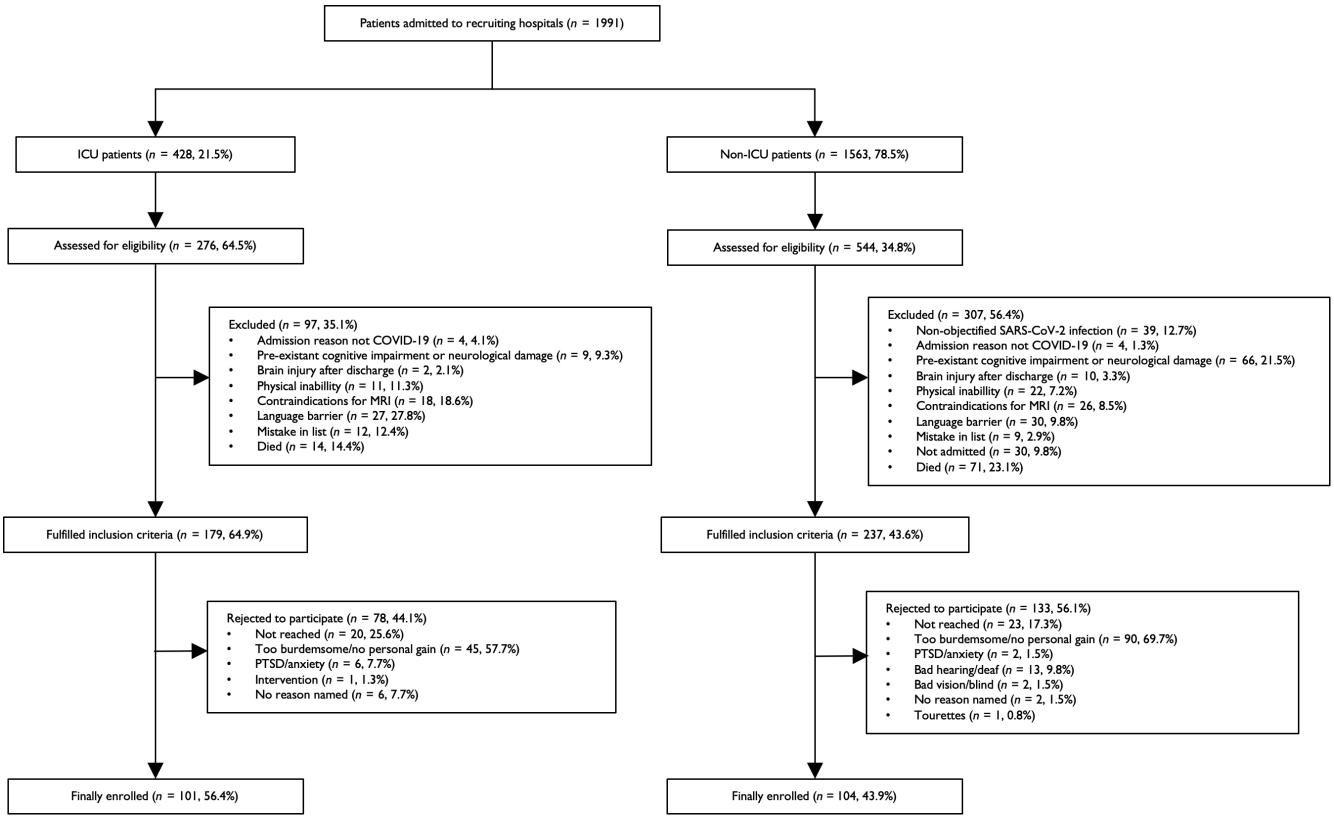

FIGURE 1 Study flowchart. Recruitment procedure: the patient selection procedure was based on lists, per recruiting hospital, including pseudonyms of all hospitalized COVID-19 patients (ICU and general ward). *Note*: The quality of ICU and non-ICU patient lists, provided by the hospitals, differed. Unlike the ICU lists, non-ICU lists included patients that died during the hospital stay and those who visited the emergency room but were not admitted. These differences influence the percentage pf excluded patients.

rate due to death (ICU 14% vs. non-ICU 23%). Additionally, non-ICU lists included patients who had visited the emergency room but were not admitted (10%). In both groups, many patients rejected participation or could not be reached. Measurements took place 8–10 months post-hospital discharge (January 2021–September 2021). The demographic and clinical characteristics of enrolled patients are shown in Table 1. The ICU group received significantly more rehabilitation after hospital discharge (all $p<0.001$) and was more often diagnosed with coagulation disorder (22% vs. 9%; $\chi^2[1, N=185]=6.53$, $p=0.01$) and delirium (47% vs. 4%; $\chi^2[1, N=181]=44.45$, $p<0.001$).

Brain abnormalities

Significantly more ICU patients had microbleeds (61%, 60/99) compared to non-ICU patients (32%, 32/99; $\chi^2[1, N=198]=15.92$, $p<0.001$); see Table 2. Also, the number of microbleeds was significantly higher in the ICU group (ICU median 1 [interquartile range 0–3] vs. non-ICU median 0 [interquartile range 0–1]; $U=3165.50$, $p<0.001$) and microbleeds occurred more often in the corpus callosum of ICU (53%, 31/58) than non-ICU patients (16%, 5/31; $\chi^2[1, N=89]=11.68$, $p<0.001$). Other MRI abnormalities did not differ.

Cognitive dysfunction

There was no significant group difference in any of the cognitive dysfunction measures (Table 3). The MoCA suggested cognitive dysfunction in 37% (37/101) of ICU patients and 44% (49/104) of non-ICU patients. The proportion of dysfunctional scores between the groups did not differ significantly either on the MoCA ($\chi^2[1, N=205]=1.23$, $p=0.27$) or on any of the neuropsychological tests or multivariate cognitive profile ($\chi^2[1, N=204]=3.30$, $p=0.07$). Whilst 41% (83/205) of the total sample scored below cut-off on the MoCA, 12% (25/204) displayed a deviant multivariate profile. Exclusion of patients (3/205) under suspicion for underperforming did not affect results. Table S4 reports the mean (SD) and median (interquartile range) per neuropsychological test.

Neurological symptoms, cognitive complaints, emotional distress and wellbeing

There was no significant difference between the groups on any of the questionnaire-measured constructs (see Table 4). Across both groups, most patients reported two newly acquired neurological symptoms, the most prominent being muscle weakness (48%, 87/183), pain (34%, 63/183) and paraesthesia (33%, 62/187). Overall,

TABLE 2 Group comparison of brain abnormalities.

Clinical feature	ICU ($n=99$)	Non-ICU ($n=99$)	p value[a]
White matter lesions[b]	1 [0–2]	1 [0–2]	0.99
Cerebral infarcts, *N* (%)	6 (6)	5 (5)	0.76
Lacunes, *N* (%)	9 (9)	16 (16)	0.13
Macrobleeds, *N* (%)	4 (2)	4 (2)	1.00
Perivascular spaces, *N* (%)	99 (100)	98 (99)	1.00
Microbleeds, *N* (%)	60 (61)	32 (32)	**<0.001**[f]
Number of microbleeds per patient[c]	1 [0–3]	0 [0–1]	**<0.001**[f]
Microbleeds in corpus callosum, *N* (%)	31 (53)[d]	5 (16)[e]	**0.001**[f]
Global cortical atrophy	1 [1–2]	1 [1–2]	0.09
Medial temporal lobe atrophy, left	1 [0–1]	1 [0–2]	0.14
Medial temporal lobe atrophy, right	1 [0–1]	1 [0–1]	0.60

Note: Values are median (interquartile range) or *N* (%). Comparisons remaining significant after Benjamini-Hochberg correction are highlighted in bold.

Abbreviations: ICU, intensive care unit; *n*, number of individuals; non-ICU, general ward patients.

[a]*p* values are uncorrected and refer to the χ^2 test or Fisher's exact test (where expected cell values were below 5) for dichotomous variables and the Mann–Whitney *U* test for continuous, non-normally distributed or categorical variables.

[b]Fazekas scale: 0, absence of white matter lesions; 1, non-confluent/punctuate; 2, beginning confluent; 3, confluent.

[c]Microbleeds: 0, none; 1, 1 microbleed; 2, 2–4 microbleeds; 3, 5–9 microbleeds; 4, 10–19 microbleeds; 5, ≥20 microbleeds.

[d]Out of patients with microbleeds $n=58$ (two missing values).

[e]Out of patients with microbleeds $n=31$ (one missing value).

[f]Comparisons that remained significant after Benjamini–Hochberg correction.

62% (122/196) of patients reported ≥3 cognitive complaints. Of all patients, 19% (36/193) had clinically relevant anxiety scores, 15% (28/193) clinically relevant depression scores and 12% (24/194) had clinically relevant post-traumatic stress symptoms. 28% (54/194) had severe insomnia and 51% (99/195) severe fatigue.

Relation between brain abnormalities and cognitive dysfunction

A simple linear regression analysis with the number of microbleeds as predictor for the averaged *t* score across cognitive tests showed no significant relationship ($\beta=0.31$, $p=0.80$).

DISCUSSION

This large-scale study investigated brain abnormalities and long-term objective and subjective consequences in ICU and non-ICU

TABLE 3 Comparison of cognitive dysfunction (classified as *z*-scores ≤−2) between the ICU and non-ICU group.

Test	ICU ($n=101$)	Non-ICU ($n=104$)	p value[b]
Global cognitive function			
Montreal Cognitive Assessment	37/101 (37)	46/104 (44)	0.27
Mental speed/attention			
Trail Making A	1/98 (1)	7/102 (7)	0.07
Stroop 1	7/99 (7)	8/103 (8)	0.85
Stroop 2	5/99 (5)	9/103 (9)	0.30
Executive function			
Trail Making B	1/96 (1)	6/101 (6)	0.12
Trail Making B/A	5/97 (5)	12/101 (12)	0.09
Stroop 3	3/97 (3)	8/102 (8)	0.14
Stroop interference (3/2)	0/97 (0)	1/102 (1)	1.00
Controlled Oral Word Association	6/99 (6)	7/103 (7)	0.83
Category Fluency (Animals)	3/100 (3)	4/104 (4)	0.74
Category Fluency (Occupations)	3/98 (3)	5/104 (5)	0.72
Working memory			
Symbol Digit Substitution	5/99 (5)	5/103 (5)	1.00
Digit Span forwards	0/99 (0)	4/102 (4)	0.12
Digit Span backwards	2/98 (2)	5/102 (5)	0.45
Memory			
Rey's Auditory Verbal Learning Task (trial 1–5)	2/98 (2)	7/104 (7)	0.11
Rey's Auditory Verbal Learning Task (delayed recall)	3/96 (3)	13/102 (13)	0.01
Rey's Auditory Verbal Learning Task (recognition)	5/97 (5)	7/102 (7)	0.61
Visuospatial function			
Judgement of Line Orientation	7/99 (7)	4/102 (4)	0.33
Language function			
Boston Naming Task	2/100 (2)	6/102 (6)	0.28
Deviant multivariate profile[a]	8/100 (8)	17/104 (16)	0.07

Note: Values are *n*/total *N* (%). None of the comparisons remained significant after Benjamini–Hochberg correction.

Abbreviations: ICU, intensive care unit; *n*, number of individuals; non-ICU, general ward patients.

[a]Based on Controlled Oral Word Association, Category Fluency (Animals and Occupations), Rey's Auditory Verbal Learning Task, Trail Making Task A and B, Stroop 1, 2 and 3.

[b]*p* values are uncorrected and refer to group differences assessed with χ^2 tests or Fisher's exact tests (where expected cell values were below 5).

TABLE 4 Comparison of the ICU (*n*=101) and non-ICU (*n*=104) group on measures of neurological symptoms, cognitive complaints, and well-being.

		ICU (*n* = 101)			Non-ICU (*n* = 104)			
Construct	**Questionnaire**	***n***	**Score**	**Below cut-off**	***n***	**Score**	**Below cut-off**	***p* value**[a]
Neurological symptoms	NeNeSCo questionnaire	95	2 [0–5]	–	99	2 [0–3]	–	0.41
Cognitive complaints	Checklist for Cognitive Consequences following Intensive Care Admission	95	4 [1–8]	–	101	3.0 [1–7]	–	0.79
Anxiety	Hospital Anxiety and Depression Scale (Anxiety subscale)	95	2 [1–6]	19 (20)	98	3 [1–6]	17 (17)	0.57
Depression	Hospital Anxiety and Depression Scale (Depression subscale)	95	2 [1–4]	13 (14)	98	3 [1–6]	15 (15)	0.07
Post-traumatic stress	Primary Care PTSD Screen for DSM-5	95	0 [0–1]	10 (11)	97	0 [0–1]	14 (14)	0.76
Physical functioning	PROMIS Physical Function (short form)	95	45 [39–49]	–	100	47 [42–51]	–	0.11
Fatigue	Fatigue Severity Scale	95	38 [27–50]	49 (52)	100	37 [26–48]	50 (50)	0.55
Insomnia symptom severity	Insomnia Severity Index	95	4 [2–9]	20 (21)	99	7 [3–12]	34 (34)	0.01
Sleep efficiency	Pittsburgh Sleep Quality Index	94	86.4 [77.4–94.1]	–	99	87.50 [77.4–95.2]	–	0.50
Subjective sleep quality	Pittsburgh Sleep Quality Index	95	1 [0–1]	–	100	1 [1–1]	–	0.01
Quality of life	EuroQol-5D-5L	94	0.8 [0.7–1.0]	–	102	0.8 [0.8–1.0]	–	0.94
Social participation	Utrecht Scale for Evaluation of Rehabilitation–Participation (Restrictions subscale)	95	92.6 [72.7–92.6]	–	97	95.8 [83.3–100.0]	–	0.07

Note: Three missing datapoints were mean imputed. Values are median [interquartile range] or *n*/total *N* (%).

Abbreviations: ICU, intensive care unit; *n*, number of individuals; non-ICU, general ward patients.

[a]*p* values are uncorrected and refer to group score differences (not to percentages below cut-off) assessed with Mann–Whitney *U* tests. None of the group comparisons remained significant following Benjamini–Hochberg correction.

COVID-19 survivors. The aim was to create a more holistic picture of COVID-19 consequences across different disciplines. In line with our hypotheses, ICU patients displayed more brain abnormalities than non-ICU patients. Specifically, cerebral microbleeds were more prevalent, had a higher number and were more frequently present in the corpus callosum. Cognitive dysfunction, neurological symptoms, cognitive complaints and wellbeing were similar across groups. The expected higher prevalence of neurological symptoms and cognitive dysfunction in the ICU group was not found. The absence of a group difference in cognitive complaints and wellbeing was expected. Domain-specific cognitive dysfunction was low in all patients. However, self-reported symptoms such as cognitive complaints, neurological symptoms and severe fatigue occurred frequently in both groups.

The pattern of extensive microbleeds affecting the corpus callosum has previously been described in non-COVID-19 ICU patients and recently also in a sample of COVID-19 ICU patients [19,20]. A systematic review on neuroimaging features of COVID-19 reported seven studies describing microbleeds in atypical locations such as the corpus callosum and juxtacortical white matter [19,21]. Whilst cause and aetiology are unclear, the extensive occurrence of microbleeds in the corpus callosum mirrors findings of high-altitude exposure and acute respiratory distress syndrome (ARDS), putting hypoxia forward as a likely contributing mechanism [20]. As severe hypoxia often necessitates ICU admission, this would explain the increased microbleed prevalence in the ICU group [22]. Supporting hypoxia as a mechanism contributing to microbleeds, a matched case–control study showed that the frequency of microbleeds is similar in COVID-19 ARDS patients and non-COVID-19 ARDS patients [23]. A second mechanism possibly involved in microbleeds is coagulopathy, which also had a greater prevalence in the ICU group [20]. These findings suggest that microbleeds are not specific to COVID-19 but have a common origin with other critical illnesses. Further, a baseline difference in microbleeds cannot be ruled out and may have been associated with a higher risk of developing a more severe disease course. Microbleeds can occur with increasing age and have been associated with hypertension and kidney function [24-26].

Similar to their aetiology, also the clinical relevance of microbleeds is not yet clear [27]. Microbleeds may be manifestations of small vessel disease, which can lead to vascular cognitive impairment. However, only few studies report cognitive dysfunction associated with microbleeds [27]. So far, no study has investigated the association between microbleeds and cognition in COVID-19 patients. Despite a difference in microbleed prevalence, our groups did not differ in cognitive dysfunction and no relationship between microbleeds and cognitive dysfunction was found, suggesting that microbleeds are clinically silent. Corpus callosum infarcts have been associated with functional decline, specifically of memory and visuospatial abilities, and attention [28]. A negative impact on these domains could therefore have been expected.

Cognitive dysfunction was similar across groups. A potential explanation for the absence of group difference is that illness severity and comorbidity differed less than expected. Both ICU and non-ICU patients had to be hospitalized, indicating serious illness, and both had similar comorbidities. As our study did not employ clinical markers of illness severity, differences could not be established. Given the fact that all patients required hospital admission, groups may have differed little in inflammatory and immune response. Due to the shortage of hospital beds in the early spring 2020 COVID-19 wave, only the most severe cases were admitted to a hospital, potentially decreasing differences between ICU and non-ICU patients. However, in contrast to non-ICU patients, all ICU patients required mechanical ventilation, which is a clear indication of more severe illness. Further, measures of illness severity of our ICU group resembled those of other studies [29].

The cognitive dysfunction screening tool (MoCA) indicated cognitive impairment in 40% of patients. However, the extent of domain-specific cognitive dysfunction was low (12% based on a deviant multivariate profile), particularly given the overrepresentation of comorbidities (e.g., hypertension, diabetes, cardiac disease) known to affect brain health and cognition [30,31]. The difference between cognitive dysfunction based on a screening tool and a standard neuropsychological test battery can be explained by test sensitivity and specificity. Screening tools are constructed to value sensitivity over specificity [32]. This leads to an overestimation of dysfunction compared to diagnostic tests, such as our standard test battery. Despite this, the difference is still striking and may be the result of our relatively strict cut-off score (i.e., $z \leq -2$) on the standard test battery or a suboptimal cut-off score of the screening tool for this specific population. Future studies should determine the cut-off point with the highest diagnostic accuracy in this population. Meanwhile, the MoCA remains a valuable clinical screening tool to separate patients without cognitive dysfunction from those in need of more elaborate cognitive testing.

Aside from an impact on cognition, critical illness can cause various other health problems. ICU patients are susceptible to developing post-intensive care syndrome, consisting of physical, cognitive and psychiatric symptoms [33]. Commonly, ICU patients suffer more emotional distress (i.e., anxiety, depression and post-traumatic stress symptoms) than non-ICU patients. However, the levels of emotional distress in our sample did not differ between groups. This may be attributable to more care, including psychological care, for ICU patients after hospital discharge. This is supported by low levels of emotional distress reported in our sample and other ICU COVID-19 studies [3,29,34]. Furthermore, ICU patients usually experience more trauma than non-ICU patients. However, all COVID-19 patients were confronted with additional stressors such as uncertainty and fear of the disease's impact on health and isolation from their social support system. These experiences probably affect ICU and non-ICU patients but may be even more impactful for the non-ICU patients who, unlike the sedated ICU patients, consciously experienced their isolated hospitalization. These factors could have led to the absence of group difference. Both groups experienced a similar and high prevalence of neurological symptoms, cognitive complaints and fatigue. This fits the growing body of research describing self-reported symptoms even after a mild disease course [35].

The percentage of individuals scoring in the abnormal range on the cognitive screening tool is similar to an earlier study [34]. However, other studies on cognitive dysfunction in COVID-19 patients reported effects on memory, attention and executive function, with some reporting a higher prevalence in more severely ill patients [7,8]. Many of these studies compared ICU or all hospitalized patients with non-hospitalized patients, allowing for a greater group difference. Furthermore, differences in sample selection, neuropsychological tests and cut-off values for cognitive dysfunction (−2SD vs. −1.5SD) may explain inconsistencies in results. Preselection of patients with cognitive complaints or neurological symptoms, as employed by some studies, could have also led to a higher prevalence of dysfunction [36]. Further, the long-term consequences were investigated whereas many studies recruited patients shortly after hospital discharge [7,37].

The high frequency of cognitive complaints in our sample, in combination with severe fatigue and persistent neurological symptoms, fit the post-COVID-19 syndrome. The World Health Organization describes this syndrome as a collection of symptoms such as fatigue, shortness of breath, loss of smell or taste, and depression or anxiety that can persist even after a mild disease course [38]. Limited cognitive dysfunction in our sample consisting of severely ill patients, as well as brain abnormalities being predominantly restricted to ICU patients, indicates that the prevalence of objective negative consequences in post-COVID-19 syndrome is low. Cognitive complaints and fatigue exceed cognitive dysfunction by far, suggesting psychosocial interventions to be of added value to cognitive rehabilitation therapy.

The strengths of our study include the combination of measurement instruments to assess the consequences of COVID-19 hospitalization on different levels of function. Not only was the impact on the brain assessed, but also direct and indirect consequences based on neuropsychological testing and self-reporting. This multidisciplinary approach leads to valuable knowledge with a broader focus, which at the same time limits the amount of detail per discipline. Secondly, the generalizability of findings was increased by adopting a multicentre approach. Finally, a non-preselected sample was recruited.

Some limitations need to be addressed. First, our study was designed in 2020 with the aim of clarifying clinical observations of neurological and neuropsychological sequelae in ICU and general ward COVID-19 patients. Whilst conducting the study, it became apparent that also mildly infected patients without the need for hospitalization develop serious long-term complaints. Including a non-hospitalized post-COVID-19 group and a control group of ICU patients without COVID-19 would have been of added value. Secondly, the recruitment process may have introduced a selection bias, as patients on both ends of the consequence spectrum may not have participated. Excluding patients unable to visit the hospital was necessary for acquiring the MRI scan. This may have excluded the most severely ill patients. However, exclusion based on this criterion was similar for both groups (11.3% for ICU and 7.2% for non-ICU) and should therefore not have influenced the absence of group differences. Similarly, patients with structural neurological damage (e.g., stroke) occurring after hospital discharge were excluded. Thirdly, our findings are based on patients of the first infection wave. Generalizability of results may be compromised by changes in treatment and viral mutations. In the second wave, the beneficial effect of immunomodulators became apparent [39]. By reducing inflammatory processes, these agents may influence the impact on the brain and associated consequences. Included patients were probably predominantly infected with the SARS-CoV-2 alpha variant [40]. The emergence of different variants may have impacted illness severity, the immune response and thereby the brain and function. Fourthly, MRI images were evaluated by a single rater. However, the rated abnormalities have been shown to have good interrater reliability [15]. Finally, some variables concerning disease and treatment characteristics (length of hospitalization, re-hospitalization) were not available but could have aided the interpretation of results.

CONCLUSION

In this large long-term follow-up study, COVID-19 ICU survivors had a higher prevalence of microbleeds than non-ICU patients. These microbleeds also occurred in greater numbers and more often in the corpus callosum. Despite this higher prevalence of microbleeds amongst ICU survivors, cognitive dysfunction was equally present in both groups. COVID-19 ICU admission, therefore, does not lead to worse cognitive functioning than does general ward admission. Cognitive complaints, self-reported neurological symptoms and severe fatigue are very frequently reported, fitting the post-COVID-19 syndrome and general post-ICU consequences. Self-reported negative consequences exceeding rates of cognitive dysfunctions suggest that psychosocial interventions are of added value to cognitive rehabilitation therapy. This information can guide clinical practice for individual patients. The findings further elicit new research questions regarding risk factors for developing persistent symptoms. A biopsychosocial approach to this question seems appropriate.

AUTHOR CONTRIBUTIONS

CMvH and JH conceptualized and designed the study. CMvH, JH, SK, JMAVM, AAD, EV and AJCS developed the study protocol. AAP designed the neuroimaging aspects of the study and evaluated the MRI images. SK was responsible for patient recruitment and data collection. SK, AAP and AAD were responsible for the statistical analysis. All authors contributed to the interpretation of data and manuscript preparation. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

D ATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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