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RESEARCH ARTICLE

Long COVID-19: Objectifying most self-reported neurological symptoms

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Abstract

Objectives: We aimed to objectify and compare persisting self-reported symptoms in initially hospitalized and non-hospitalized patients after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by applying clinical standardized measures. **Methods**: We conducted a cross-sectional study of adult patients with confirmed SARS-CoV-2 infection including medical history, neurological examination, blood markers, neuropsychological testing, patient-reported outcome measures (PROMs), and brain magnetic resonance imaging (MRI). **Results**: Fifty patients with persisting symptoms for at least 4 weeks were included and classified by initial hospitalization status. Median time from SARS-CoV-2 detection to investigation was 29.3 weeks (range 3.3–57.9). Although individual cognitive performance was generally within the normative range in both groups, mostly mild deficits were found in attention, executive functions, and memory. Hospitalized patients performed worse in global cognition, logical reasoning, and processes of verbal memory. In both groups, fatigue severity was associated with reduced performance in attention and psychomotor speed tasks ($r_s = -0.40$, $p < 0.05$) and reduced quality of life (EQ5D, $r_s = 0.57$, $p < 0.001$) and with more persisting symptoms (median 3 vs. 6, $p < 0.01$). PROMs identified fatigue, reduced sleep quality, and increased anxiety and depression in both groups but more pronounced in non-hospitalized patients. Brain MRI revealed microbleeds exclusively in hospitalized patients ($n = 5$). **Interpretation**: Regardless of initial COVID-19 severity, an individuals' mental and physical health can be severely impaired in the long-term limitedly objectified by clinical standard diagnostic with abnormalities primarily found in hospitalized patients. This needs to be considered when planning rehabilitation therapies and should give rise to new biomarker research.

Introduction

Long COVID-19 syndrome refers to signs and symptoms that persist or newly develop 4 weeks after a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[1] with "ongoing symptomatic COVID-19" describing persisting symptoms 4–12 weeks after infection and "Post-COVID-19 syndrome" with symptoms exceeding 12 weeks.

Several international large-scale studies identified a substantial extent of neuropsychiatric long-term symptoms including fatigue, cognitive complaints, headache, anxiety, and depression, some of which can persist up to 7 months

post-infection[2–4] and have been reported by both, mild and severe acute COVID-19 patients. While many studies focused on single aspects of *Long COVID-19* symptomatology, studies bringing together objective neuropsychological, imaging, and clinical data are sparse so far and have been mainly conducted in initially hospitalized COVID-19 patients, although long-term sequalae also manifest in younger, less comorbid individuals, free from chronic metabolic, cardiovascular, and pulmonary diseases.[5,6]

Regarding the frequent cognitive problems, commonly used cognitive screens in affected individuals were largely normal, while more detailed testing revealed impairments especially in alertness and concentration, attention, and executive functions in initially hospitalized and non-hospitalized patients.[7–10] For neuropsychiatric sequalae, a comprehensive meta-analysis found that a COVID-19 diagnosis increases the likelihood of a psychiatric diagnosis in the following months also when compared to equally severe diseases.[11,12]

Neuroimaging studies investigating SARS-CoV-2-related brain pathologies have largely been performed in severe cases requiring hospitalization and subsequent brain imaging during acute COVID-19 primarily picturing acute events.[13] However, very early preprint studies indicate subtle structural and functional changes detected by specialized quantitative imaging analyses in non-hospitalized patients as well.[14,15]

To sum up, qualitative studies covering the different aspects of the *Long COVID-19* spectrum contextualizing imaging, neuropsychological and clinical findings in a clinical feasible setting are urgently needed to help physicians and patients properly manage the disease.

In our study, we used a comprehensive standard clinical diagnostic approach including neurological examination, standardized neuropsychological testing, blood markers, patient-reported outcome measures (PROMs), and multimodal MRI in initially hospitalized and non-hospitalized patients.

Facing an increasing number of *Long COVID-19* patients, our aim is to objectify most common neurological long-term sequelae across distinct patient groups providing valuable information towards a standardized diagnostic work-up and treatment of *Long COVID-19* patients. We expect a greater impact on cognitive performance, quality of life, and brain imaging in hospitalized patients pointing to distinct rehabilitation strategies tailored to this patient group in the long-term.

Methods

Design and participants

We performed a cross-sectional analysis of an ongoing longitudinal prospective observational study initiated in August 2020 at the Department of Neurology, RWTH Aachen University Hospital in Germany. Here, we report on the first 50 included patients, grouped in initially hospitalized (n = 21) and non-hospitalized (n = 29) patients during acute COVID-19. Eleven patients needed intensive care treatment, 4 of which received extracorporeal membrane oxygenation (ECMO). Importantly, only patients with persisting symptoms for at least 4 weeks were included. Patients were recruited either from the Department of Neurology (neurological COVID-19 outpatient clinic or inpatient ward), the Department of Pneumology and Intensive Care Medicine (Department of Internal Medicine V), or the Department of Cardiology, Angiology and Intensive Care Medicine (Department of Internal Medicine I) of the RWTH Aachen University Hospital. Eleven patients of our previous study on acute neurological features in hospitalized patients were included in our current study.[16] Patients were eligible to participate if they were older than 18 years and able to consent. Almost all patients (n = 49) had a SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction of nasopharyngeal swab and one by the presence of SARS-CoV-2-antibodies without previous vaccination. All visits were performed between August 13, 2020 and March 30, 2021.

Standard protocol approvals, registrations, and patient consents

The study was reviewed and approved by the Ethics Committee of the Medical Faculty of RWTH Aachen University (EK192/20). Informed consent was obtained verbally and in written form from every participant.

Procedures

Neurological examination, clinical interview, and laboratory markers

A complete neurological examination and a structured interview was performed by an attending neurologist to identify current and past acute symptoms (i.e., symptoms occurring up to 4 weeks after positive SARS-CoV-2 test).

Laboratory markers were analyzed by our house-internal central laboratory available either from blood samples collected as part of the study or from clinical records and included: C-reactive protein (CRP), procalcitonin, soluble interleukin-2 receptor (sIL-2R), tumor necrosis factor alpha (TNFα), ferritin, antithrombin III, fibrinogen, D-dimers, folic acid, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides.

Cognitive assessment

Major cognitive domains including attention and psychomotor speed, executive functions, language,

visuospatial processing, and memory, were assessed using a common standardized neuropsychological testing battery. The Montreal Cognitive Assessment (MoCA, version 7) was used for global screening.[17] Cued and not-cued reaction times (RTs) were measured through the alertness subtest of the Test of Attentional Performance (TAP).[18] The Trail Making Test (TMT)[19] parts A and B provided indexes on processing speech and cognitive flexibility. We measured the span of immediate verbal recall and auditory working memory using the digit span forwards and backwards. Verbal fluency, both semantic and phonemic modalities (using either the CERAD-Plus battery[20] or the Regensburger Wortflüssigkeit-Test, RWT)[21] assessed functions related to language production and executive functions. A Stroop test variant (Farbe-Wort-Interferenztest, FWIT)[22] was used as a measure of selective attention and inhibitory control. The Auditory Verbal Memory Test (VLMT)[23] or the wordlist subtest from the CERAD-Plus battery were used to assess verbal episodic memory. Rey-Osterrieth complex figure test (ROCFT)[24] or the figure subtest from CERAD-Plus was used to assess visual perception and construction (figure copy) and visual memory (30-min delayed recall for ROCFT or delayed free figure recall for CERAD-Plus). The Boston Naming Test (CERAD-Plus) was used to assess confrontation naming.

Impairment was defined as performance below a percentile rank (PR) of 16, with severe impairment classified as PR below 2, according to published adjusted-normative data (depending on test for age, education, and/or sex). Olfaction was tested using the identification subtest of the Burghart Sniffin' Sticks**,** comprising of 16 common odorants with multiple forced-choice.[25]

Patient-reported outcomes measures

PROMs assessed affective symptoms (Hospital Anxiety and Depression Scale, HADS-D),[26] health status (EQ-5D 5-level), fatigue (Fatigue Scale for Motor and Cognitive Function, FSMC),[27] sleep quality (Pittsburgh Sleep Quality Index, PSQI),[28] daytime sleepiness (Epworth Sleepiness Scale, ESS),[29] and level of autonomy in basic everyday motor functions and self-care skills (Extended Barthel Index, EBI).[30] For the HADS-D, the following cut-off scores regarding severity of symptoms in each of the sub-scales were considered: ≤7 normal, 8–10 questionable, ≥10 increased. Severity of fatigue assessed by the FSMC total score was categorized as mild fatigue (≥43), moderate fatigue (≥53), or severe fatigue (≥63).[27] PSQI total score was calculated for the previous 4 weeks according to the original scoring instructions.[28] The cut-off for daytime sleepiness according to the ESS was >10.[31]

MRI data acquisition and analyses

MRI scans were performed on a 3 Tesla PRISMA MR scanner (Siemens Medical Systems, Erlangen, Germany) including the following sequences: T1-weighted, T2-weighted, DWI, SWI, FLAIR. Due to research MRI contraindications, scans (at 1.5 T and T2* instead of SWI) from clinical records were used for four patients. All MRI scans were independently rated by K. R. and A. S. C., blinded to clinical information, using the following visual rating scales: unified four-point atrophy scale for orbitofrontal, rostral anterior cingulate, anterior temporal, frontoinsular, medial temporal, and posterior regions, ARWMC for age-related brain white matter changes, and for enlarged perivascular spaces (EPVS).[32–34] Cerebral microbleeds were rated using a four-point interval scale (0 = none, 1 = 1, 2 = 2–4, 3 = 5–10, and 4 = ≥10 microbleeds) for infratentorial, deep, lobar and corpus collosum regions. The presence and location of macrohemorrhages, cortical superficial siderosis, ischemic lesions, and other abnormalities (trauma, tumor, inflammation, edema, hydrocephalus) were also documented.

Statistical analysis

Categorical variables are presented as count (percentage) and continuous variables as mean (standard deviation) or median (interquartile range). We computed composite scores without data imputation by averaging the normative age and/or education percentile-rank-scores for *a priori* defined cognitive domains: attention, executive functions, language, visuospatial processing, verbal memory, and non-verbal memory. The use of parametric or non-parametric approaches followed distribution normality, tested using the Kolmogorov–Smirnov test. Chi-square test, Fisher's exact test, or Mann–Whitney *U*-Test was used to assess differences between hospitalization status. To control for covariates in between group analyses, we conducted additional exploratory analysis of covariances. Association measures were calculated using Spearman's rank correlation coefficients. Test statistics were transformed in effect sizes and Cohen's classification was used for size interpretation: <0.3 = small, 0.3–0.5 = medium, and 0.9 to infinity = large.

We built logistic regression models to control for age effects in the risk of abnormalities in neuroimaging regarding hospitalization status. Missing data were not imputed.

Statistical analyses were done with R version 4.0.4, Python programming language (version 3.7.7, with packages pandas 1.2.4, seaborn 0.11.1, matplotlib 3.4.2, pingouin 0.3.11 and scipy 1.6.3). All tests were two-sided with a p value of 0.05 set as the threshold for significance.

Data availability statement

Individual de-identified participant data that underlie the results reported in this article and the study protocol will be shared upon reasonable request.

Results

Medical history including self-reported acute and long-term symptoms

The clinical characteristics of the 50 (n) patients are presented in Table 1. The median (Mdn) age was 50.5 years (range 22–84 years), 21 (42%) participants had been initially hospitalized and 28 (56%) were female. The median timespan after infection for non-hospitalized patients was 13.43 weeks (range 3.3–57.86) and 41 weeks (range 18.14–52.29) for hospitalized patients. Male patients were significantly more frequent in the hospitalized group (n = 14 vs. n = 8; p = 0.014). Average time since infection was 29.3 weeks (range 3.29–57.86) for all patients with 15.79 weeks (range 3.3–51.71) for female and 40.5 weeks (range 10–57.86) for male patients. According to the NICE Guidelines, the majority of subjects (76%) presented with a post-COVID-19 syndrome and 23% patients with ongoing symptomatic COVID-19.

The most common comorbidities included arterial hypertension (36%), followed by dyslipidemia and obesity (14% each). Proportion of arterial hypertension and use of respective medication and ex-smoking was higher in the hospitalized group. Most frequent pre-existing neuropsychiatric conditions included migraine (12%) and depression (8%).

Although still within the normal range, hospitalized patients had elevated levels of inflammatory markers, including, CRP, procalcitonin, TNFα, and sIL-2R when compared to non-hospitalized patients (Table S1). This group was also significantly associated with altered lipid metabolism markers, including elevated levels of triglycerides and reduced levels of HDL-cholesterol.

Self-reported acute and long-term symptoms are presented in Figure 1. During acute COVID-19, the most frequently reported symptom was an altered sense of smell and/or taste (74%), particularly in non-hospitalized patients. Patients reporting smell disturbances showed more severe affective symptoms (HADS Mdn 17 vs. 9, U = 447.5, $p < 0.01$). Fatigue was the second most common complaint (66%), followed by general flu symptoms (64%) including chills, overall body aches and feeling sick, cough (56%), fever (54%), dyspnea (50%), and headache (50%). Fever and dyspnea were more common in hospitalized patients in the acute phase.

During *Long COVID-19*, cognitive complaints were most frequently (70%) reported. In particular, patients frequently referred difficulties in attention and concentration (56%), with a higher proportion in non-hospitalized patients, followed by memory complaints (38%), and word-finding problems (18%). Furthermore, subjective cognitive complaints were more frequent in patients reporting more severe affective symptomatology (HADS Mdn 13 vs. 7, U = 341.5, $p < 0.05$).

Fatigue was the second most common (62%) long-term symptom. Interestingly, patients reporting fatigue did not show worse scores in the FSMC (Mdn 67 vs. 56.6, U = 269, p = 0.126). According to the FSMC scores, patients reporting moderate to severe fatigue (FSMC score ≥53, n = 28) express significantly more symptoms in the long-term (Mdn 6), when compared to patients with no or mild fatigue (n = 13, FSMC Score <53, Mdn 3; $p < 0.01$). Other frequent long-term symptoms included smell and/or taste disturbances (52%), sleep problems (44%), and headache (22%), the later with a higher proportion in non-hospitalized patients and women (p = 0.01).

Clinical examination including olfactory testing

Neurological signs and conditions diagnosed after COVID-19 infection are shown in Table 2. The frequently self-reported olfactory and gustatory long-term alterations encompass, hyposmia (34%), anosmia (12%), and parosmia (12%), as well as hypogeusia (28%), parageusia (22%), and ageusia (12%). Olfactory function was formally tested in 43 patients, from which 21 (49%) reported a subjective disturbance in form of hyp-, par-, or anosmia. Eleven (26%) of the 43 tested patients showed an impaired performance in the Sniffin' Stick identification subtest, according to age normative references. In fact, performance was similar for patients with and without subjective smell disturbances (6 vs. 5 patients with abnormal results, χ^2 = 0.072, p = 0.79). Other frequent findings of neurological examination were difficulties in tandem walk (26%) and sensory deficits (22%), primarily in hospitalized patients. Likewise, severe pallesthesia (i.e., measured ≤4/8 bimalleolar) and gait abnormalities were more often found in hospitalized patients (respectively, 10% and 8%). The most frequent neurological condition diagnosed after COVID-19 was critical illness polyneuropathy/critical illness myopathy (CIP/CIM) diagnosed by a neurologist and/or confirmed by electrophysiology (n = 3) in 9 (43%) of the hospitalized patients.

Patient-reported outcome measures

PROMs are shown in Table 3. Non-hospitalized patients tend to have higher levels of anxiety (Mdn HADS-A score

Table 1. Clinical characteristics of 50 patients according to hospitalization status.

	Total (n = 50)	Non-hospitalized (n = 29)	Hospitalized (n = 21)	p value
Age (in years), median (IQR)	50.5 (41–61)	45.6 (37–56)	57.3 (52–62)	0.01
Education: years, median (IQR)	15.5 (12.75–18)	16 (13–18)	13 (12–16)	<0.01
Sex (female)	28 (56%)	21 (72.4%)	7 (33.3%)	0.01
Cardiovascular risk factors				
Arterial hypertension	18 (36%)	7 (24.14%)	11 (52.38%)	0.08
Dyslipidemia	7 (14%)	2 (6.90%)	5 (23.81%)	0.12
Obesity	7 (14%)	4 (13.79%)	3 (14.29%)	1
Ex-smoking	7 (14%)	2 (6.90%)	5 (23.81%)	0.01
Current smoking	6 (12%)	4 (13.79%)	2 (9.52%)	0.13
Diabetes Type II	6 (12%)	2 (6.90%)	4 (19.05%)	0.22
Atrial fibrillation	1 (2%)	1 (3.45%)	0 (0%)	1
Other[1]	6 (12%)	2 (6.90%)	4 (19.05%)	0.22
Pre-existing conditions				
Migraine	6 (12%)	3 (10.34%)	3 (14.29%)	0.69
Depression	4 (8%)	1 (3.45%)	3 (14.29%)	0.30
Brain tumor[2]	3 (6%)	3 (10.34%)	0 (0%)	0.25
Head trauma	3 (6%)	1 (3.45%)	2 (9.52%)	0.57
History of stroke/TIA	2 (4%)	2 (6.90%)	0 (0%)	0.50
Dementia	2 (4%)	0 (0%)	2 (9.52%)	0.17
Movement disorder	1 (2%)	0 (0%)	1 (4.76%)	0.42
Epilepsy	1 (2%)	1 (3.45%)	0 (0%)	1
Other[3]	16 (30%)	9 (31.03%)	7 (33.33%)	1
Medication				
Antihypertensive	20 (40%)	8 (27.59%)	12 (57.14%)	0.09
Statins	6 (12%)	2 (6.90%)	4 (19.05%)	0.22
Anticoagulant	5 (10%)	1 (3.45%)	4 (19.05%)	0.15
Antidepressant	4 (8%)	1 (3.45%)	3 (14.29%)	0.30
Anticonvulsant	4 (8%)	2 (6.90%)	2 (9.52%)	1
Immunosuppressant	3 (6%)	3 (10.34%)	0 (0%)	0.25
Other[4]	22 (44%)	11 (37.93%)	11 (52.38%)	0.47

Date are presented as median (IQR) or n (%). Chi-square test, Fisher's exact test and Mann–Whitney U-Test were used. TIA, transient ischemic attack; IQR, interquartile range.

[1]Including coronary heart disease (n = 2), cardiovascular surgery (n = 2), carotid artery stenosis (n = 1), myocardial infarction (n = 1).

[2]Including meningioma (n = 2) and vestibular schwannoma (n = 1).

[3]Including thyroid disease (n = 2), asthma (n = 2), valve- and/or heart insufficiency (n = 4), autoimmune disease (n = 2), chronic obstructive pulmonary disease (n = 2).

[4]Including antidiabetic, analgesic, antidementia, antihistamines, thyroid hormone therapy, proton pump inhibitors, hypolipidemic, asthma medication, alpha-1-receptor-blockers.

7.0 vs. 6.0) and more severe fatigue (Mdn total FSMC Score 67.00 vs. 56.50) compared to hospitalized patients. Importantly, the severity of fatigue assessed by FSMC was significantly associated with reduced quality of life (EQ5D, $r_s = 0.57$, $p < 0.001$). Sleep quality (PSQI, cut-off value 5), was reduced similarly in both groups (Mdn score 9.5 and 10.0). Patients reporting sleep problems more frequently showed worse scores on PSQI (Mdn score 10.5 vs. 7, $U = 229$, $p < 0.05$) and also worse health status (EQ5D Mdn 0.76 vs. 0.92, $U = 144.5$, $p < 0.05$). Regarding their best imaginable health status, the self-report was slightly worse in non-hospitalized patients (EQ-VAS, Mdn 64.44% vs. 71.42%). Basic everyday motor functions and self-care skills, were preserved in both groups (EBI, Mdn score 64.00) although hospitalized patients tend to have more problems in mobility (47.61% vs. 31.03%) and self-care (19.05% vs. 3.45%) (Table S3). We found no association between clinical characteristics, e.g., vascular risk factors, and affective symptoms (HADS), fatigue (FSMC), or other health indicators (e.g., EQ-5D, ESS).

Neuropsychological assessment

Compared to non-hospitalized patients, hospitalized patients perform worse in MoCA (Mdn total uncorrected score: 25 vs. 27.5, $U = 146.0$, $p < 0.05$, $d' = 0.25$), logical reasoning and specific processes of verbal memory, such

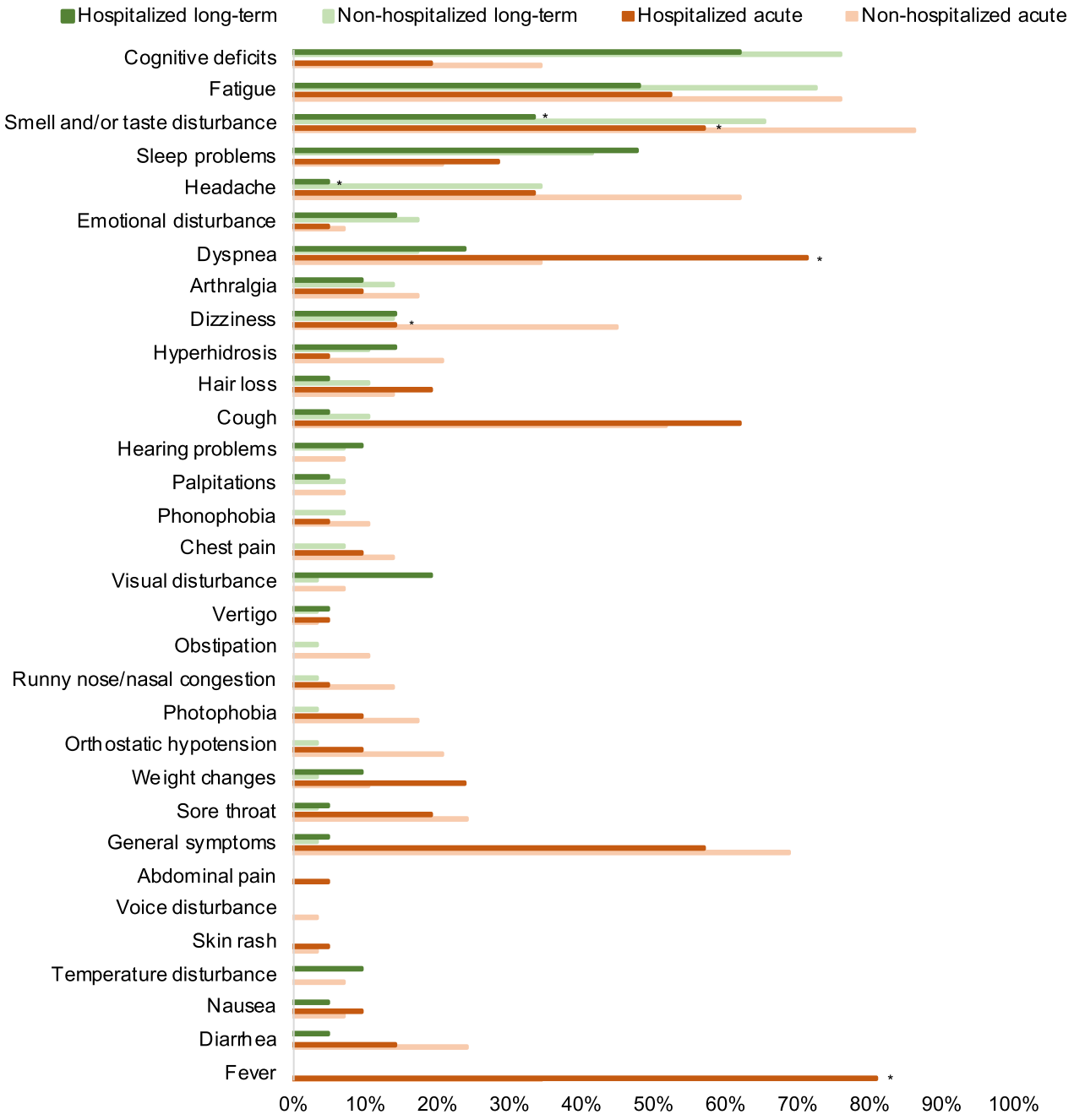

Figure 1. Self-reported acute and long-term symptoms of 50 patients with COVID-19 according to hospitalization status. The diagram shows the percentage of self-reported acute and long-term symptoms of respective hospitalization group. Group comparison was calculated between hospitalized and non-hospitalized patients using chi-square test or Fisher's exact test. Symptoms are ordered according to the frequency of long-term symptoms in non-hospitalized patients. Significant differences ($p < 0.05$) between both groups are indicated by asterisks and included smell and/or taste disturbance, dyspnoea, dizziness, and fever during acute COVID-19 and smell and/or taste disturbance and headache for long-term symptoms.

as first trial learning and total learning. At least for the memory tasks, this difference is influenced by age ($F(1, 46) = 5.722$, $p < 0.05$). Sex distribution did not affect group differences.

Overall, neuropsychological performance was within standard normative references, according to age and/or education published norms, with PR values above 16 (Table 4). Independently of hospitalization status, there

Table 2. Neurological signs and conditions diagnosed after COVID-19 infection.

	Total (n = 50)	Non-hospitalized (n = 29)	Hospitalized (n = 21)	p value
Smell disturbance*	23 (46%)	18 (62%)	5 (24%)	<0.01
SS-16 abnormal[1]	11 (22%)	8 (28%)	3 (14%)	0.49
Taste disturbance*	23 (46%)	16 (55%)	7 (33%)	0.15
Memory impairment*	19 (38%)	9 (31%)	10 (48%)	0.45
Word-finding problems*	9 (18%)	3 (10%)	6 (29%)	0.24
Attention problems*	28 (56%)	20 (69%)	8 (38%)	0.06
Paresthesia*	6 (12%)	4 (14%)	2 (10%)	0.82
Sensory deficit*	11 (22%)	2 (7%)	9 (43%)	<0.01
Pallasthesia (≤4/8)	5 (10%)	0 (0%)	5 (24%)	<0.01
Impaired fine motor skills	6 (12%)	2 (7%)	4 (19%)	0.38
Paresis	6 (12%)	3 (10%)	3 (14%)	0.69
Abnormal reflex status	6 (12%)	3 (10%)	3 (14%)	0.81
Gait abnormality	4 (8%)	0 (0%)	4 (19%)	0.03
Difficulties in tandem walk	13 (26%)	3 (10%)	10 (48%)	<0.01
Neurological conditions diagnosed after COVID-19 infection				
Stroke/TIA	3 (6%)	1 (3%)	2 (10%)	0.57
Seizures	1 (2%)	0 (0%)	1 (5%)	0.42
CIP/CIM	9 (18%)	0 (0%)	9 (43%)	<0.001

Data are presented as n (%). For group comparison Chi-square test or Fisher's exact test was used. Asterisks indicate self-reported symptoms. TIA, transient ischemic attack; CIP/CIM, critical illness polyneuropathy/critical illness myopathy.
[1]Sniffin' Stick identification test to assess olfactory function. Missing data (n = 7).

was a tendency for worse performance in attention, psychomotor speed and memory tasks (Fig. 2). Performance below normative references (PR <16) was primarily found in TAP cued RT (47.5%), phonemic verbal fluency (44%), non-verbal free delayed recall (36.7%), and verbal free delayed recall (32.6%). Rates of severe impairment (PR <2) were low for TAP cured RT (3%) and phonemic verbal fluency (7%), whereas both in non-verbal free delayed recall and verbal-free delayed recall impairment would be classified as mild in all patients with performance below the normative reference. In contrast, no patient showed impairment in logic reasoning or in the Stroop interference task. These proportions were similar for hospitalized and non-hospitalized patients.

In the whole group, worse performance in attention and psychomotor speed tasks was associated with increased fatigue scores (Fig. 3) in the FSMC ($r_s = -0.40$, $p < 0.05$), and specifically in the FSMC motor domain ($r_s = -0.52$, $p < 0.01$) but not the FSMC cognitive domain ($r_s = -0.28$, $p = 0.08$). Although the severity of affective symptoms (HADS total score) was positively associated with total fatigue ($r_s = 0.49$, $p < 0.001$), it was not associated with performance in attention and psychomotor speed tasks ($r_s = -0.28$, $p = 0.06$). The association between fatigue and performance in attention and psychomotor tasks remained negatively associated when controlled for education and HADS total score ($r_s = -0.53$, $p < 0.01$). In turn, worse performance in attention and psychomotor speed was also associated with worse health status (EQ5D, $r_s = 0.53$, $p < 0.05$) and excessive daytime sleepiness (ESS, $r_s = -0.41$, $p < 0.05$). Comparisons between the remaining cognitive composites (Table S2) and PROMs yielded no further associations. Similarly, cognitive performance was neither associated with clinical characteristics, such as time since infection, nor with frequently reported symptoms such as smell disturbance (subjective and olfaction test performance), sleep problems, perceived fatigue, or even cognitive dysfunction.

Visual MR ratings

Visual ratings of cortical atrophy generally corresponded to a mild widening of the sulci (score rating 1) and did not differ between groups (Table 5). Results from association measures between atrophy scores and clinical outcomes were not significant, after controlling for outliers.

White matter hyperintensities (WMH) were rare in both groups but, when present, represented focal lesions (score rating 1) in periventricular regions. No associations were found between the severity of WMH and clinical outcomes. EPVS were similar in both groups and rated as moderate in centrum semiovale and classified as mild in the basal ganglia. We also found no associations with clinical outcomes. In contrast, cerebral microbleeds were more frequent (21.4%) and solely found in hospitalized patients and almost only in those (n = 4) who received extracorporeal membrane oxygenation support. Further analyses revealed no independent contribution of age to the

Table 3. Patient-reported outcome measures after COVID-19.

	Total (n = 50)	Non-hospitalized (n = 29)	Hospitalized (n = 21)	Missing data	p value
Affective symptoms					
Depression, HADS[1]	5.08 (3.45)	5.38 (3.13)	4.67 (3.87)	0	0.29
Normal (≤7)	39 (78%)	22 (75.86%)	17 (80.95%)		0.74
Increased (>7)	11 (22%)	7 (24.14%)	4 (19.05%)		0.74
Anxiety, HADS	6.88 (4.41)	7.62 (4.59)	5.86 (4.04)	0	0.20
Normal (≤7)	28 (56%)	15 (51.72%)	13 (61.91%)		0.57
Increased (>7)	22 (44%)	14 (48.28%)	8 (38.1%)		0.57
Quality-of-life measures					
FSMC[2], total	61.8 (19.03)	64.26 (17.04)	57.07 (22.31)	9	0.22
Normal (<43)	8 (16%)	4 (13.79%)	4 (19.05%)		0.41
Mild (≥43)	5 (10%)	3 (10.34%)	2 (9.52%)		1
Moderate (≥53)	7 (14%)	4 (13.79%)	3 (14.29%)		0.67
Severe (≥63)	21 (42%)	16 (55.17%)	5 (23.81%)		0.20
FSMC, motor	30.37 (9.52)	31.04 (8.48)	29.07 (11.51)	9	0.50
Normal (<22)	7 (14%)	4 (13.79%)	3 (14.29%)		0.67
Mild (≥22)	6 (12%)	3 (10.34%)	3 (14.29%)		0.40
Moderate (≥27)	7 (14%)	5 (17.24%)	2 (9.52%)		1
Severe (≥32)	21 (42%)	15 (51.72%)	6 (28.57%)		0.52
FSMC, cognition	31.44 (10.37)	33.22 (9.61)	28 (11.25)	9	0.14
Normal (<22)	10 (20%)	5 (17.24%)	5 (23.81%)		0.27
Mild (≥22)	5 (10%)	3 (10.34%)	2 (9.52%)		1
Moderate (≥28)	6 (12%)	3 (10.34%)	3 (14.29%)		0.39
Severe (≥34)	20 (40%)	16 (55.17%)	4 (19.05%)		0.1
PSQI[3]	9.25 (3.84)	9.21 (4.09)	9.33 (3.47)	14	0.77
Good sleepers (≤5)	5 (10%)	4 (13.79%)	1 (4.76%)		0.65
Poor sleepers (>5)	31 (62%)	20 (68.97%)	11 (52.38%)		0.65

Data presented as mean (standard deviation) or n (%).Test results based on Mann–Whitney U-test or Fisher's exact test. FSMC, Fatigue Scale for Motor and Cognitive Function; PSQI, Pittsburgh Sleep Quality Index.

[1]Hospital Anxiety and Depression scale (HADS). Scores ≤7 are normal, scores between 8 and 10 indicate slightly increased anxiety or depression.

[2]Fatigue Scale Motor Cognition to assess cognitive and motor fatigue. Total scores ≥43 indicate mild fatigue, ≥53 moderate fatigue and ≥63 severe fatigue. Motor fatigue scores ≥22 indicate mild fatigue, ≥27 moderate fatigue and ≥32 severe fatigue. Cognition fatigue scores ≥22 indicate mild fatigue, ≥28 moderate fatigue and ≥34 severe fatigue.

[3]PSQI to assess subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping pills, and daytime sleepiness. Total score results can vary from 0 to 21, whereby a higher score corresponds to a reduced sleep quality. Cut-off value of 5 allows a division into "good" and "poor" sleepers.

presence of cerebral microbleeds in hospitalized patients, but suggest an association, regardless of localization, with worse visuospatial processing (infratentorial: $r_s = -0.12$, $p < 0.05$, deep: $r_s = -0.40$, $p < 0.01$, lobar: $r_s = -0.43$, $p < 0.01$, corpus callosum: $r_s = -0.42$, $p < 0.01$).

Discussion

In this prospective observational study, we comprehensively analyzed and compared long-term manifestations of 50 COVID-19 patients after mild and severe acute COVID-19. Our results suggest that the type and frequency of symptoms change over the disease course and that 6 months after infection a myriad of neurological symptoms might still be frequently reported by both, non-hospitalized and hospitalized COVID-19 patients. As persisting symptoms, most frequently reported symptoms in both groups were problems with cognition and fatigue followed by sleep problems in hospitalized patients and impaired functioning of taste and smell in non-hospitalized patients. With the exception of fatigue, we found no clear evidence of generalized impairment on objective testing of olfactory function or cognitive functioning. Noteworthy, severity of fatigue was more increased in non-hospitalized patients and associated with more long-term symptoms. Furthermore, abnormalities in laboratory findings and neuroimaging were primarily found in hospitalized patients in form of altered lipid and inflammatory markers, and microbleeds. Independently of hospitalization status, neuropsychological performance was generally within normative range. However, there was a trend to worse performance in attention and psychomotor speed tasks. Patients also frequently presented clinically relevant affective symptoms, particularly anxiety,

Table 4. Neuropsychological performance after COVID-19.

	Total (n = 50)		Non-hospitalized (n = 29)		Hospitalizd (n = 21)				
Neuropsychological measures (PR)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Test result	p value	d'
Attention and psychomotor speed									
TAP simple RT (Intrinsic alertness)	40	31.7 (22.8)	25	30.8 (22.6)	15	31.5 (23.9)	190.0	0.96	0.51
TAP cued RT (phasic alertness)	40	23.5 (16.8)	25	22.1 (15.3)	15	25.2 (19.6)	200.5	0.73	0.53
TAP Go/NoGo RT	29	51.0 (29.3)	17	51.1 (27.8)	11	50.9 (33.2)	93.0	1.0	0.49
TAP divided attention, visual RT	24	65.4 (23.3)	15	70.1 (15.6)	9	57.6 (32.0)	53.0	0.40	0.39
TAP divided attention, auditory RT	24	32.8 (22.1)	15	29.9 (23.8)	9	37.7 (19.1)	84.0	0.34	0.62
TAP divided attention, omissions	24	51.2 (26.1)	15	52.3 (26.6)	9	49.3 (26.7)	64.0	0.86	0.47
TMT A – time	50	50.6 (25.9)	29	49.1 (25.1)	21	52.8 (27.4)	332.0	0.59	0.54
Executive functions									
TMT B – time	49	44.1 (27.9)	29	45.1 (24.4)	20	42.8 (33.2)	260.0	0.55	0.45
Phonemic verbal fluency	50	33.7 (29.2)	29	38.3 (32.1)	21	27.4 (23.9)	253.5	0.32	0.42
Stroop interference – time	34	65.9 (21.6)	23	69.8 (21.4)	11	58.0 (20.6)	85.0	0.13	0.34
Logical reasoning	36	66.2 (25.4)	24	73.5 (21.3)	12	52.9 (27.6)	71.0	0.03	0.27
Digit span backwards	38	54.4 (28.5)	25	57.4 (28.4)	13	48.8 (28.9)	137.0	0.44	0.42
Language									
CERAD+ Naming	37	47.9 (27.9)	26	44.2 (25.1)	21	52.5 (31.0)	337.5	0.17	0.62
Semantic verbal fluency	50	39.0 (25.9)	29	39.8 (28.4)	21	37.9 (22.8)	313.5	0.89	0.51
Visuospatial processing									
CERAD+ figure copy	14	46.5 (37.5)	5	64.8 (34.4)	9	36.3 (37.0)	13.5	0.25	0.30
ROCFT figure copy	36	65.1 (26.3)	24	68.1 (27.1)	12	59.2 (24.7)	109.0	0.24	0.38
Verbal memory									
Digit span forwards	38	47.5 (31.3)	25	52.1 (30.3)	13	38.6 (32.6)	116.5	0.16	0.36
VLMT first trial	36	40.1 (26.8)	24	48.1 (25.8)	12	23.9 (21.9)	67.5	<0.01	0.23
VLMT total learning	36	52.8 (29.8)	24	61.3 (29.9)	12	35.9 (22.2)	74.0	<0.05	0.26
CERAD+ total learning	14	33.5 (26.7)	5	58.4 (25.1)	9	19.7 (15.5)	3.5	<0.05	0.07
VLMT interference list	36	36.6 (32.9)	24	41.7 (37.2)	12	26.8 (20.7)	118.5	0.50	0.43
VLMT immediate delayed recall	36	49.1 (29.9)	24	56.0 (30.4)	12	35.3 (24.5)	83.0	<0.05	0.29
VLMT delayed recall	36	48.3 (32.8)	24	55.6 (35.2)	12	33.7 (22.0)	94.0	0.09	0.33
VLMT delayed recall savings	36	44.4 (30.8)	24	46.3 (30.5)	12	40.8 (32.5)	126.0	0.56	0.44
CERAD+ delayed recall savings	14	39.8 (33.3)	5	39.0 (27.9)	9	40.2 (37.6)	23.0	1.0	0.51
VLMT recognition	36	46.2 (23.6)	24	48.3 (22.2)	12	41.1 (27.5)	84.5	0.67	0.45
CERAD+ recognition	14	40.4 (30.0)	5	50.4 (25.8)	9	34.7 (32.2)	20.5	0.08	0.46
Non-verbal memory									
CERAD+ figure delayed recall	14	50.3 (35.7)	5	58.2 (36.9)	9	45.9 (36.5)	16.5	0.46	0.37
ROCFT figure delayed recall	35	31.6 (23.1)	23	34.5 (24.7)	12	25.9 (19.3)	113.5	0.30	0.39

Data presented as PRs according to normative data adjusted for demographic variables. Results below PR 16 are impaired. Test results based on Mann–Whitney *U*-Test. PR, percentile rank; ROCFT, Rey-Osterrieth Complex Figure Test; RT, reaction time; TAP, Test of Attentional Performance; TMT, Trail Making Test; VLMT, Verbal Learning Memory Test.

decreased sleep quality and health status more pronounced in non-hospitalized patients.

There was no correlation between the severity of acute COVID-19 disease, as defined by hospitalization status, and *Long COVID-19* disease outcomes assessed in our study. Abnormalities found in hospitalized patients could be mainly attributed to ICU therapy-related effects, including CIP/CIM associated symptoms, higher levels of inflammatory markers, and cerebral microbleeds. In this group, altered lipid markers and a larger proportion of patients with arterial hypertension indicated increased cardiovascular risk factors. Noteworthy, men were considerably more frequent in the hospitalized group, which is in line with previous studies, that identified male sex as a risk factor for ICU admission.[35] Furthermore men have been enrolled in our study at a substantially later time point than female patients, possibly due to an extended hospital and rehabilitation stay after severe COVID-19 of the more frequent hospitalized male patients. Given that most patients were recruited in our outpatient clinic this could also be a reporting bias, since women tend to seek medical advice more commonly and earlier than men.

The pattern of persisting symptoms reported by patients included in this study is largely in agreement with previous data describing fatigue, headache, cognitive

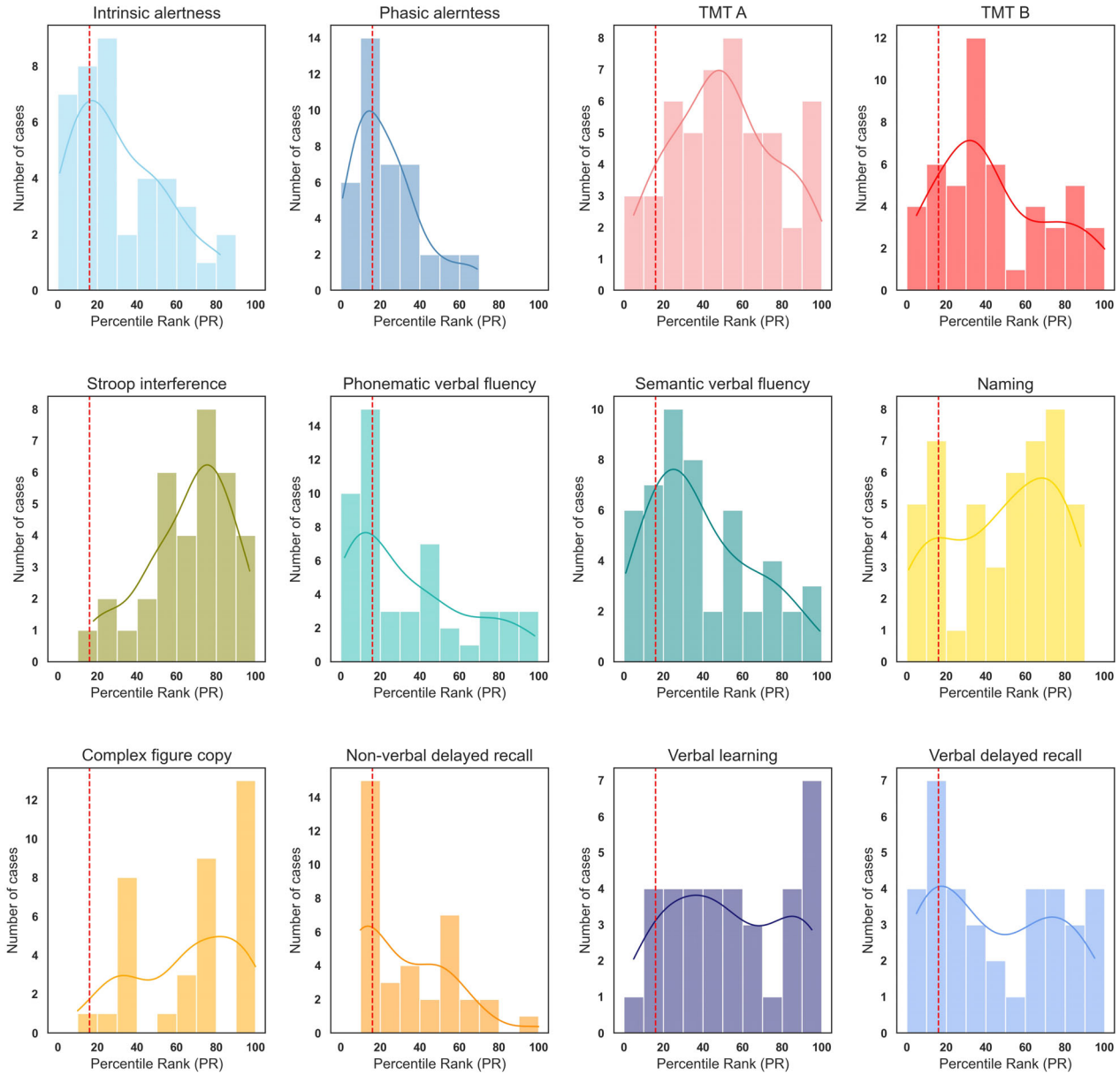

Figure 2. Neuropsychological performance of patients after COVID-19. Performance in neuropsychological tasks shows an increased dispersion between cognitive domains. Performance is tendentially impaired in time-based tasks (e.g., alertness tasks, verbal fluency, or trail making test). Overall, neuropsychological test results lie above PR 16 according to published norms adjusted for demographics and, therefore, within normative references.

deficits, and dyspnea lasting up to 7 months in up to 10% of patients post COVID-19[2,3] independent of initial hospitalization status.[6] This clearly underlines the fact that there is a shift from mainly respiratory disease during acute COVID-19 to also neurological manifestations in the long-term the proportion of which was found to be rather small during acute infection primarily including inflammatory and cerebrovascular events.[36,37] Thus, a comprehensive diagnostic work-up of the frequent neurological symptoms in the long-term is urgently needed to decrease *Long COVID-19* morbidity.

So far, Huang et al conducted the largest in-person follow-up study and identified fatigue or muscle weakness, sleep difficulties and anxiety or depression as most frequent persisting symptoms in, however, only patients hospitalized due to COVID-19.[38] Our study further contributes to the deeper characterization of such persisting manifestations by providing evidence resulting from

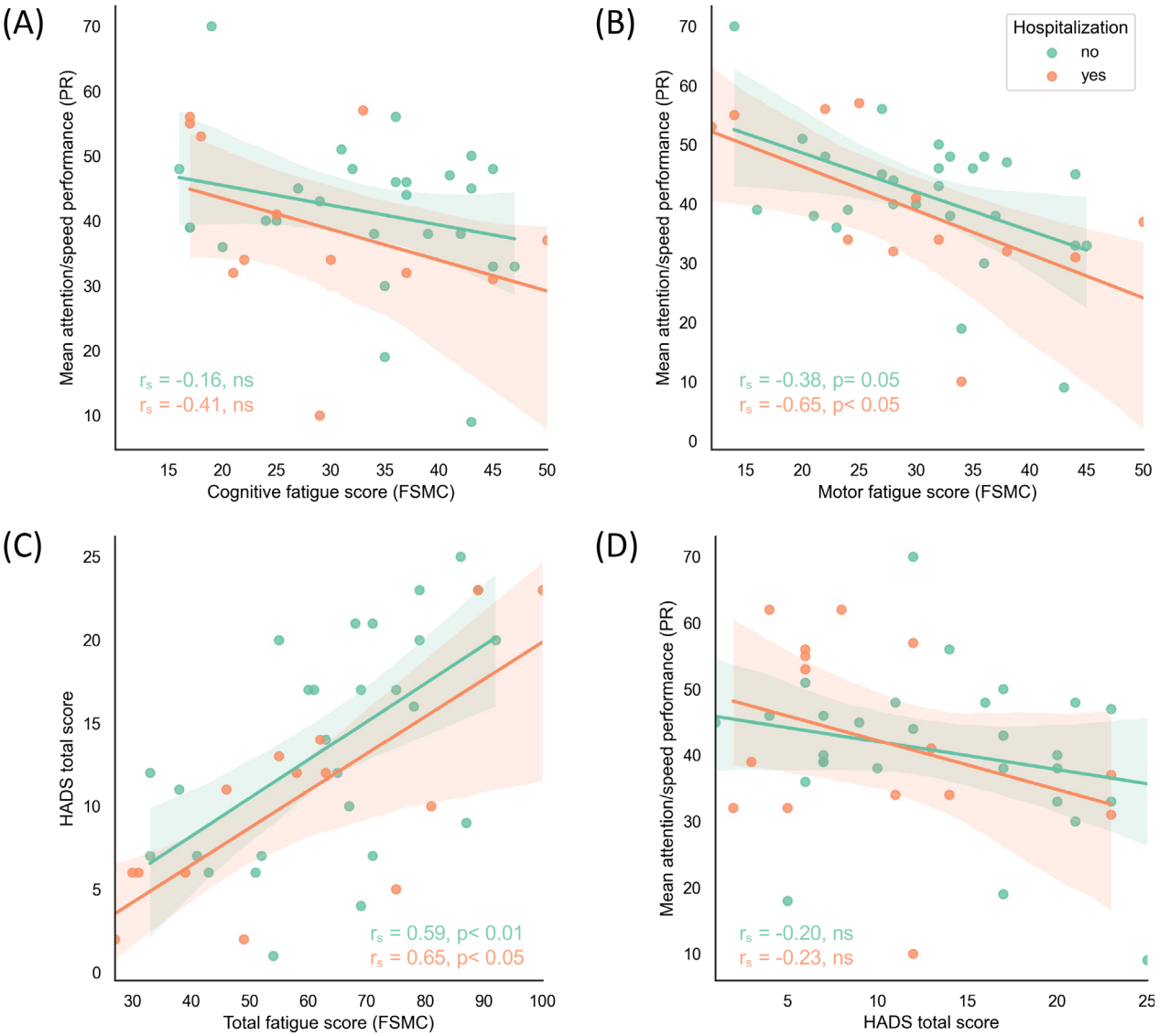

Figure 3. Association between performance in attention and psychomotor speed tasks (mean composite score) and fatigue scores (FSMC) and affective symptoms (HADS) according to hospitalization status. Performance in attention and psychomotor speed tasks, as mean composite of age and/or education normative PR scores, was negatively associated with increase scores in motor fatigue self-report (FSMC, [A and B]) in hospitalized (orange) COVID-19 patients. The severity of affective symptoms (HADS, [C]) was positively associated with the severity of fatigue (FSMC) in both hospitalized and non-hospitalized (green) patients. Affective symptoms were not associated with performance in attention and psychomotor speed task (D). FSMC, Fatigue Scale for Motor and Cognitive Function; HADS, Hospital Anxiety and Depression Scale.

objective and standardized measures, including neurological examination, neuropsychological and olfactory testing, brain MRI, and PROMs, that objectify neurological abnormalities after a mean period of ca. 6 months after SARS-CoV-2 infection.

In our study, sensory disturbances, gait difficulties, and balance problems were prominent in hospitalized patients rather attributable to well-known ICU-acquired weakness accounting probably for permanent disabilities in up to 10–15% of patients 2 years after ICU-therapy than virus-induced effects, for example, by critical illness neuropathy and myopathy. Otherwise, neurological examination revealed no evidence for deficits. Remarkably, this was also the case for olfactory functioning, which, however, agrees with a recent study showing that objective testing of olfaction poorly reflected self-reported smell disturbance, indicating that patients may underestimate the return of normosmia after SARS-CoV-2 infection.[39]

In both the groups, patients reported a reduced health status, as evidenced by decreased quality of sleep,

Table 5. MRI visual rating scores per hospitalization status after COVID-19.

Visual rating score	Total (n = 42)	Non-hospitalized (n = 22)	Hospitalized (n = 20)	p value
Atrophy (≥2)				
Orbitofrontal	1 (2.4%)	0 (0%)	1 (5%)	0.49
Rostral anterior cingulate	3 (7.3%)	0 (0%)	3 (15%)	0.11
Anterior temporal	2 (4.8%)	0 (0%)	2 (10%)	0.23
Fronto-insular	6 (14.6%)	1 (4.7%)	5 (25%)	0.09
Medial temporal	1 (2.4%)	0 (0%)	1 (5%)	0.49
Posterior	3 (7.3%)	0 (0%)	3 (15%)	0.11
White matter hyperintensities (≥2)				
Periventricular	7 (17%)	2 (9.5%)	5 (25%)	0.41
Basal ganglia	1 (2.4%)	0 (0%)	1 (5%)	0.49
Perivascular spaces (≥2)				
Centrum semiovale	24 (58.5%)	11 (52.3%)	13 (65%)	0.53
Basal ganglia	2 (4.8%)	0 (0%)	2 (10%)	0.23
Cerebral microbleeds (≥1)				
Infratentorial	6 (14.6%)	0 (0%)	6 (30%)	<0.01
Deep	7 (17%)	0 (0%)	7 (35%)	<0.05
Lobar	9 (21.9%)	0 (0%)	9 (45%)	<0.001
Corpus callosum	7 (17%)	0 (0%)	7 (35%)	<0.05

Data presented as n (%). Group comparisons calculated using Fisher's exact test. MRI, magnetic resonance imaging.

increased fatigue, which was also associated with more reduced quality of life, and frequent affective symptoms, as anxiety and depression. However, non-hospitalized patients displayed a more severe fatigue and affective symptomatology. Previous studies had shown that anxiety rates appear to be higher in non-hospitalized patients, further emphasizing that acute stages may independently contribute to *Long COVID-19* disease severity regarding neuropsychiatric sequelae.[40,41] This could also be due to a distorted perception of the symptoms during the course of the disease: while hospitalized COVID-19 survivors tend to experience a gradual improvement of their symptoms after severe acute illness with subsequent hospital release and rehabilitation, patients after mild initial disease are often unexpectedly affected by long-term symptoms and may perceive the progression from the acute phase as worsening over time.

Regarding cognitive performance, we mostly found mild deficits in attention, processing speed and memory. Only a few patients showed severe impairment in particular tasks, namely attention and executive functions. Although hospitalized patients did perform worse in MoCA, logical reasoning and specific processes of verbal memory, such as first trial learning and total learning, cognitive performance was largely comparable between hospitalized and non-hospitalized patients and mostly revealed no impairment. This profile is similar to previous reports on post-acute status of hospitalized COVID-19 patients and congruent with known cognitive outcomes of patients following critical illness and ARDS.[7,9,42,43] However, a very recent study found impairments in executive functioning, processing speed, category fluency, memory encoding, and recall to be predominant among hospitalized patients 7.2 month after COVID-19 infection.[10] Similarly, Hampshire et al revealed significant cognitive deficits in people who had recovered from COVID-19 versus controls with pronounced deficits in hospitalized patients.[44] In this study, the degree of deficits increased with the level of treatment received for respiratory difficulties, a distinction that could not be made in our study due to the small sample size, probably accounting for the overall similar cognitive performance between both groups.

Following the largely inconspicuous cognitive functioning, MRI-based visual ratings of cortical atrophy, WMH, and EPVS were to a great extent within commonly accepted normal clinical references. An exemption here was the frequent presence of cerebral microbleeds that, with the exception of one patient with a known amyloidosis, exclusively occurred in hospitalized patients that required ECMO. This is a not a novel association but adds to the amount of literature, including a meta-analysis of neuroimaging findings of 2125 patients during acute COVID-19 showing that ICU care was associated with significantly higher incidences of microvascular pathology, with a predilection for the corpus callosum, cerebral microhemorrhages, and encephalitis/encephalopathy.[13,32]

Taken together, there is a discrepancy between the frequently reported complaints and what we have been able to objectify on the basis of standard imaging, neuropsychological and olfactory measurements. However, regarding the severeness of patient-reported outcomes, this should raise the question of whether standard measurement methods and analyses are sensitive enough to detect even subtle functional and organic changes with a major impact on everyday life. Although visual inspection of structural MRI excluded macrostructural abnormalities, deeper examination of functional connectivity, structural changes, and brain metabolism may reveal the neural correlates underlying frequently reported neurological complaints. First quantitative MRI imaging studies provide evidence of altered brain integrity[15,45] and alterations in orbitofrontal and temporal brain regions[14] possibly underlying these abnormalities during the post-acute phase. The discrepancy between self-reported symptoms and objective measurements should hence not diminish

the importance of *Long COVID-19*, but further fuel our research efforts to understand its neurobiology.

Limitations of our study are a small sample size and the lack of a control group. As most of our patient were recruited from our COVID-19 outpatient clinic of the Department of Neurology, there is a reporting bias for neurological manifestations and underrepresentation of other types of possible symptoms (e.g., pulmonary). Another major limitation of our study is the lack of quantitative neuroimaging analyses, which are likely needed to detect subtle neuronal changes not evident by visual evaluation.

However, the strengths of our study are the thorough clinical, neuropsychological, behavioral and imaging approach. Thus, our study provides valuable and timely in-depth analysis of neuropsychiatric functioning across distinct domains and hospitalization course, which are needed to further develop existing guidelines for informed prognosis, counseling, long-term monitoring, and so far symptom-oriented treatment management of COVID-19 survivors. In addition to cognitive training focusing on attention and executive functioning, future therapeutic strategies should emphasize physical rehabilitation and cardiovascular risk optimization in hospitalized patients and psychotherapeutic - and educational concepts in non-hospitalized patients.

In conclusion, persistent cognitive complaints and fatigue are frequently reported symptoms irrespective of initial hospitalization status during acute COVID-19. Objectification by means of standard clinical measurements is limited, indicating the need for further in-depth analyses and novel biomarkers to bridge the diagnostic gap in *Long COVID-19* affected individuals.

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Conflict of Interest

There is no potential competing interest to be stated by the authors.

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Supporting Information

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

Table S1. Blood markers of 50 patients according to hospitalization status.
Table S2. Composite scores of neuropsychological performance after COVID-19.
Table S3. Patient-reported outcome measures after COVID-19.

