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BRIEF REPORT

Cognitive Impairment 13 Months After Hospitalization for COVID-19

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This study assessed cognitive function 13 months after hospital discharge for coronavirus disease 2019 (COVID-19), using computer-based cognitive tests. Compared to population norms, 14%–25% of patients were impaired in each dimension, and 53% had cognitive impairment in 1 or more of 4 tests. There was some association with acute COVID-19 disease severity.

Keywords. cognition; cohort study; COVID-19; epidemiology; SARS-CoV-2.

Cognitive impairment has been reported after treatment in intensive care units, in chronic lung conditions, and after various infections including severe acute respiratory syndrome coronavirus 2 [1–4]. After coronavirus disease 2019 (COVID-19), media have reported frequent complaints of persistent cognitive dysfunction or "brain fog." However, few studies have reported on objective cognitive tests with >1 year of follow-up, and most studies used simple screening tests [5, 6]. Recent studies, using more comprehensive tests, reported cognitive sequelae during hospitalization [7], 2–3 months after hospitalization [8, 9], and 4–7.6 months after COVID-19 infection, comprising hospitalized and nonhospitalized patients [10].

This study reports results from tablet-based cognitive tests about 13 months after hospitalization for COVID-19 in a large Norwegian hospital, focusing on comparison with population norms and the association with initial COVID-19 severity.

METHODS

Study Design

In total, 256 patients ≥18 years of age from 6 hospitals participated in a longitudinal observational study, Patient-Reported Outcomes and Lung Function After Hospitalization for COVID-19 (PROLUN). The study recruited all consecutive patients who were admitted until 1 June 2020 [11]. Consents were obtained 4–8 weeks postdischarge. Baseline variables during acute COVID-19 were collected by review of the electronic medical record. Comorbidity was scored using the Charlson Comorbidity Index (CCI) [12]; the score was categorized as 0 vs ≥1. Disease severity was defined using a World Health Organization ordinal scale from 0 (uninfected) to 8 (dead) [13]. The relevant categories for the hospitalized patients in this study were as follows: 3, hospitalized, no oxygen therapy; 4, oxygen by mask or nasal prongs; 5, noninvasive ventilation or high-flow oxygen; 6, intubation and mechanical ventilation; 7, ventilation plus additional organ support. These categories were collapsed to 3, 4, and 5–7.

The present study was a substudy conducted in 1 of the 6 participating hospitals, Akershus University Hospital. At the 12-month visit, we carried out neurocognitive tests in this hospital. In total, 108 patients were eligible for follow-up here.

Cognitive Tests

The patients completed a tablet-based battery of 1 warm-up task and 4 cognitive tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd, Cambridge, United Kingdom) [14]. The system has been validated in a variety of neurological and psychiatric conditions, including in Norway [15–17]. The 4 tests were (1) delayed matching to sample (DMS), testing short-term memory, visuospatial processing, learning, and attention; (2) One Touch Stockings of Cambridge (OTS), testing executive function, including higher-level thinking and decision-making processes; (3) rapid visual information processing (RVP), testing sustained attention; and (4) spatial working memory (SWM), testing working memory and strategy. The battery was normed to take 34 minutes to complete (Supplementary Table 1).

Statistical Analysis

We report cognitive test results as *z*-scores for comparison with age-, sex-, and education-adjusted norms from the United Kingdom, as provided by the vendor [18]. Because of skewed distributions, we present median *z*-scores. We compared the distributions of *z*-scores with norms ($z = 0$, standard deviation [SD] = 1) using Wilcoxon signed-rank test. We defined cognitive impairment in a domain as *z*-score < -1.5, corresponding

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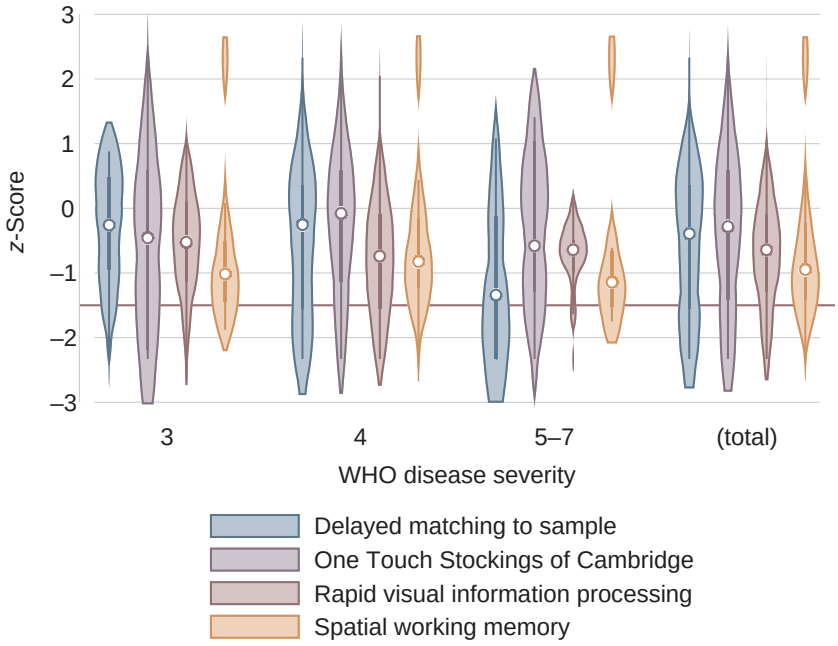

Figure 1. Distribution of cognitive function scores on 4 tests, showing *z*-scores (medians, 25th and 75th percentiles) compared to age-, sex-, and education-adjusted norms. Abbreviation: WHO, World Health Organization.

to the 6.7th percentile of the standard normal distribution. This is similar to definitions used elsewhere [10, 19].

We estimated prevalence rates of cognitive impairment and assessed the association between disease severity and cognitive impairment using logistic regression models. In a supplementary multivariable regression analysis, we also adjusted for CCI score (0 vs ≥1). We used Stata version 17.0 software (StataCorp, College Station, Texas) for all analyses.

Patient Consent Statement

All participants provided written informed consent on paper or a secure web application. The study was approved by the Regional Ethics Committee for South-Eastern Norway (number 2020/125384) and the Data Protection Officer at Akershus University Hospital.

RESULTS

Of 108 patients eligible for the follow-up visit, 86 participated, and 75 (69%) completed cognitive tests a median of 396 days (range, 352–465 days) after hospitalization for COVID-19. For logistical reasons, the first 9 patients were not tested at the 12-month visit, 1 declined, and 1 was unable to use a tablet. The patients' mean age was 55.7 years (SD, 13.7 years) and 43 (57%) were male. In total, 24 (32%) had no supplementary oxygen during their initial hospital stay, 38 (51%) had supplementary oxygen only, and 13 (17%) had high-flow oxygen, noninvasive ventilation, or intubation with ventilator support. Further details on the patients are presented in Supplementary Table 2.

The median cognitive test *z*-scores were, overall and across all COVID-19 disease severities, below 0 for each of the 4 domains and close to −1 for SWM (Figure 1). The distributions of *z*-scores were significantly lower than norms, with $P = .048$ for OTS and $P < .001$ for the other 3 tests, although the reductions were fairly small. The median *z*-scores ranged from −0.28 for OTS to −0.95 for SWM, corresponding to the 39th and 17th percentiles, respectively, of the standard normal distribution.

The prevalence of cognitive impairment on the respective tests was as follows: DMS, 19 of 75 (25%); OTS, 18 of 75 (24%); RVP, 15 of 73 (21%); and SWM, 10 of 74 (14%). In total, 40 of 75 (53%) had cognitive impairment on at least 1 test.

Severe COVID-19 was associated with a higher risk of impairment in the DMS domain in logistic regression analysis (odds ratio, 9.43 [95% confidence interval, 1.54–57.74]) compared to non-oxygen-treated patients (Table 1). Disease severity did not significantly affect the other cognitive domains. Adjusting for comorbidity (CCI score 0 vs ≥1) only marginally influenced the odds ratios and did not change the level of significance (Supplementary Table 3).

DISCUSSION

In this study, survivors after hospitalization for COVID-19 scored lower than norms on the selected cognitive tests of short-term memory, working memory, attention, and executive function. Although the reductions in general were small, for these domains 14%–25% of the patients had scores suggesting

Table 1. Association Between World Health Organization 8-Point Ordinal Disease Severity and Impaired Cognitive Performance (*z*-Score < −1.5), Logistic Regression Analysis (N = 75)

	4 Versus 3 (Referent)				5–7 Versus 3 (Referent)			
Cognitive Test	No.	Odds Ratio	(95% CI)	*P* Value	No.	Odds Ratio	(95% CI)	*P* Value
Delayed matching to sample	38	4.48	(.90–22.38)	.068	13	9.43	(1.54–57.74)	.015
One Touch Stockings of Cambridge[a]	38	0.45	(.14–1.47)	.187	13	0.60	(.13–2.81)	.52
Rapid visual information processing[a]	37	3.89	(.77–19.69)	.101	13	3.15	(.45–21.95)	.25
Spatial working memory[b]	38	0.43	(.09–2.11)	.30	12	1.67	(.31–9.04)	.55

World Health Organization disease severity: 3 (referent), hospitalized, no oxygen therapy; 4, oxygen by mask or nasal prongs; 5, noninvasive ventilation or high-flow oxygen; 6, intubation and mechanical ventilation; 7, ventilation plus additional organ support.

Abbreviation: CI, confidence interval.

[a]n = 73.

[b]n = 74.

impairment, defined as *z*-score < −1.5, compared to 6.7% as expected from the norm population. Those with severe COVID-19 scored lower on the DMS task than non-oxygen-treated patients.

There may be several explanations for this apparent impairment, and it is not clear that this is related to the COVID-19 infection. It is possible that this could be explained by premorbid conditions or comorbidities, living in the epidemic, or psychological sequelae; however, this could not be determined in the present study.

This study had a longer time to follow-up than reported in previous studies [5, 8–10, 20]. Assessments were done after about 13 months, when most patients would have recovered from the acute disease.

The cognitive patterns reported here support previous reports, albeit these having shorter follow-up. Deficits were found in 5 of 8 domains after 8 months in hospital patients vs outpatients (attention, executive functioning, category fluency, and memory) and 2 of 8 domains for emergency department patients vs outpatients (category fluency and memory encoding) [10]. The proportion of patients with deficits ranged from 13% to 39% across the 8 tests, compared to 14%–25% across 4 tests here; both studies defined impairment as *z*-score < −1.5. Our findings are also similar to findings from telephone-administered neuropsychological tests in 137 survivors as early as 2 months after hospitalization for COVID-19, where 6%–38% had moderate impairment (*z*-score < −1) in separate domains, and 59% impairment in at least 1 domain [8]. Similarly, among 130 patients tested 3 months after hospital discharge, only 19% of patients showed normal cognition across tested domains [9], although more detailed comparison with that study was not possible. Finally, the findings suggest worse cognitive performance according to disease severity, as previously reported after 4 months by contrasting intensive care unit patients with nonhospitalized patients [20]. Differences in findings between studies may be due to differences in populations, assessment methods, definition of impairment, comparison groups, and time between COVID-19 onset and assessment. Research on cognitive impairments after COVID-19 may be at an early stage, and recently detailed, standardized neuropsychological evaluations of COVID-19 patients in diverse populations after hospitalization have been requested [21].

Some study limitations should be noted. Because we had no information on or assessments of cognitive function in the participants prior to COVID-19 infection, and therefore, one should careful about postulating causality, we cannot tell whether cognitive impairments were new late onset or persistent. Furthermore, we did not have reliable information on previous anxiety or depression, which may be associated with cognition. Choice of comparison group in cognitive testing remains a challenge for interpretation of findings following COVID-19. Very few studies would have pre–COVID-19 cognitive tests for the same individuals, and in case, this would probably be because there was a special indication. Other options would be to have a non–COVID-19 group from the general population, or possibly hospitalized for another reason for comparison. The choice of control group could in any case be criticized, and there may be proponents of different choices. We had no non–COVID-19 control group, and there are no available Norwegian norms. Therefore, we used established UK norms for the cognitive tests for comparison. These norms have been provided by the vendor [18]. These norms were derived from web-based cognitive assessment from a UK population ≥18 years of age, with no previous significant head injury (resulting in loss of consciousness), no mental health condition that is uncontrolled (by medication or intervention) and that has a significant impact on daily life, and no previous diagnosis of mild cognitive impairment or dementia [18]. We think these norms represent a feasible comparison for patients after COVID-19, when a local control group is not available.

The sample size was limited, thereby precluding extensive multivariable analysis; however, the *z*-scores adjust for age, sex and education. Because of attrition, we cannot exclude bias in the prevalence rates. These data were from a single hospital, limiting generalization to other contexts. Furthermore, these patients were recruited during the first wave of COVID-19, and sequelae after later waves may be different.

We do not have COVID-19 subtypes for the patients in in the present study. Based on a limited national sample, the dominating subtype during this period was B.1, and less commonly B.1.1 and B.1.1.1 [22]. None of the patients were vaccinated prior to COVID-19, as the vaccines were not yet authorized.

In conclusion, we found signs of cognitive impairments in several domains as long as 13 months after hospitalization for COVID-19. With visual pattern recognition and nonverbal visual memory, there was an association with acute COVID-19 disease severity. This should be ascertained in larger studies and with even longer observation times.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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