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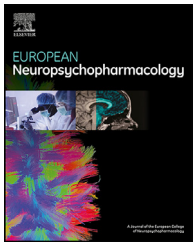

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Trajectory of cognitive impairments over 1 year after COVID-19 hospitalisation: Pattern, severity, and functional implications

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quaLity of life

Abstract
The ongoing Coronavirus Disease (COVID-19) pandemic has so far affected more than 500 million people. Lingering fatigue and cognitive difficulties are key concerns because they impede productivity and quality of life. However, the prevalence and duration of neurocognitive sequelae and association with functional outcomes after COVID-19 are unclear. This longitudinal study explored the frequency, severity and pattern of cognitive impairment and functional implications 1 year after hospitalisation with COVID-19 and its trajectory from 3 months after hospitalisation. Patients who had been hospitalised with COVID-19 from our previously published 3-months study at the Copenhagen University Hospital were re-invited for a 1-year

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follow-up assessment of cognitive function, functioning and depression symptoms. Twenty-five of the 29 previously assessed patients (86%) were re-assessed after 1 year (11±2 months). Clinically significant cognitive impairments were identified in 48-56 % of patients depending on the cut-off, with verbal learning and executive function being most severely affected. This was comparable to the frequency of impairments observed after 3 months. Objectively measured cognitive impairments scaled with subjective cognitive difficulties, reduced work capacity and poorer quality of life. Further, cognitive impairments after 3 months were associated with the severity of subsequent depressive symptoms after 1 year. In conclusion, the stable cognitive impairments in approximately half of patients hospitalized with COVID-19 and negative implications for work functioning, quality of life and mood symptoms underline the importance of screening for and addressing cognitive sequelae after severe COVID-19.

Introduction

The ongoing pandemic caused by the SARS-CoV-2 virus (COVID-19) has so far affected more than 500 million people worldwide. A key concern is the frequent lingering physical, cognitive, neurological or psychiatric symptoms that persist for 12 or more weeks after the recovery from acute illness and are collectively referred to as 'long-COVID', or 'post-COVID syndrome' (NICE., 2021). While studies have shown that even asymptomatic or mild infection may lead to persistent symptoms (Bliddal et al., 2021; de Graaf et al., 2021), the risk appears to be greater amongst those with severe COVID-19 illness (Nakamura et al., 2021; Schou et al., 2021; Taquet et al., 2021a), older age and greater comorbidity (Ceban et al., 2022). Accordingly, studies indicate that the frequency of long-COVID symptoms is 20-40 % in general (Bliddal et al., 2021; Llach and Vieta, 2021; Logue et al., 2021), but up to 85% for patients who have been hospitalised with COVID-19 (Vejen et al., 2022). Given this high prevalence of lingering symptoms, inter-disciplinary long-COVID clinics have been established to address the needs of these patients.

Long-term cognitive sequalae of COVID-19, also coined cognitive COVID, involve fatigue, 'brain fog', memory and concentration difficulties. Meta-analytic evidence indicates that cognitive COVID occurs in 20-30% of people with COVID-19 in general (Ceban et al., 2022) and in around 30% of hospitalized COVID-19 patients (Nakamura et al., 2021; Schou et al., 2021), with executive function, memory, and attention being most affected (Nakamura et al., 2021; Schou et al., 2021). Further, a large-scale internet-based study with > 80,000 patients with or without COVID-19, suggested executive dysfunction of substantial effect size, 6-months after infection in both hospitalized and non-hospitalized patients (Hampshire et al., 2021). Notably, estimates of cognitive impairments varied across the included original studies, likely due to differences in the sensitivity of the implemented cognitive test batteries (including MoCA, MMSE, SCIP, WAIS-IV) (Schou et al., 2021). We found, using a sensitive cognitive screener devoid of ceiling effects in populations with work-related stress (Jensen et al., 2022) or psychiatric conditions (Ott et al., 2021), that 59-65 % of hospitalized patients displayed clinically significant verbal learning and memory, executive function and working memory impairments 3 months after hospital discharge (Miskowiak et al., 2021). The biological mechanisms underlying these cognitive symptoms are likely multifactorial; Acute and ongoing systemic inflammation due to autoimmunity complications, direct viral invasion of the central nervous system due to leakiness of the blood-brain-barrier (Pajo et al., 2021; Proal and VanElzakker, 2021) and cerebral microhaemorrhages, as identified by white matter hyperintensities, may all play a key role (Baldini et al., 2021; Mazza et al., 2021; Moonis et al., 2020; Scardua Silva et al., 2021). From a biopsychosocial perspective, additional contributing factors to cognitive COVID may be the social aspect of having a serious illness, stigma, and isolation and inactivity related to the pandemic (Grover et al., 2021; Sykes et al., 2021).

The duration of cognitive COVID and long-term impact on functioning and quality of life are unclear. One study of hospitalized patients ($n = 312$) indicated little to no cognitive improvement within the first 6 months, with observations of cognitive impairments in 79% and 75% of patients after 3 months and 6 months, respectively (Poletti et al., 2021). Another longitudinal study found that overall, 47 % of patients had cognitive impairments. Specifically, 21% had memory impairments, 12% had executive dysfunction 1 year after hospitalisation (Méndez et al., 2022). A third study identified concentration difficulties in 31 % of patients 1 year after hospital discharge (Becker et al., 2021). Notably, 45 % of patients in the latter study, who had no prior history of psychiatric illness, reported psychiatric morbidity and poorer quality of life following COVID-19 (Méndez et al., 2022). This is comparable to a large-scale study ($n = 236\ 379$), which demonstrated that within 6 months after COVID-19, 38 % of hospitalised patients received a neuropsychiatric diagnosis (14 % with first onset), most commonly depression or anxiety (Taquet et al., 2021b). This co-occurrence of cognitive and psychiatric sequelae of COVID-19 is noteworthy given pre-existing evidence for close links between cognitive and depressive symptoms (Nys et al., 2006; Weiland-Fiedler et al., 2004; Weisenbach et al., 2012). This raises the possibility that these symptoms are interlinked. Indeed, cognitive impairment is a key contributor to functional impairment and mood symptoms across several neuropsychiatric illnesses (Cambridge et al., 2018; Mitchell et al., 2014; Woo et al., 2016), whereas depressive symptoms may also exacerbate cognitive impairments (McDermott and Ebmeier, 2009).

The present longitudinal study of patients hospitalized with COVID-19 aimed to explore (I) the frequency, pattern, and severity of cognitive impairments 1 year after hospitalisation with COVID-19, (II) the trajectory of cognitive impairments from 3 months to 1 year after hospitalisation, (III) the association between cognitive impairments, functioning and quality of life, and (IV) whether cognitive impairments 3 months after hospitalisation are associated with subsequent depression symptoms after 1 year.

Methods

Participants and recruitment

Participants were recruited to take part in a prospective follow-up study 'IMPACT-COVID' examining all adult patients ($\geq$ 18 years) admitted with COVID-19 to Bispebjerg Hospital in Denmark from March 2020 until the end of the first wave of COVID-19 cases in July 2020 (Johnsen et al., 2021). COVID-19 diagnosis was confirmed upon hospitalisation based on a positive polymerase chain reaction (PCR) test for SARS-CoV-2 from the upper respiratory tract or a positive IgG titer for COVID-19. Participants were recruited as part of their 3-months post discharge assessment of physical and cognitive functions (see Johnsen et al 2021; Miskowiak et al 2021). Participants were excluded from the study if they presented insufficient Danish language abilities or pre-existing neurological comorbidities. Prior to data collection, regional ethics committee in the Capital Region of Denmark approval was obtained for all study procedures (protocol no. H-20035553). All participants provided informed written consent prior to study enrolment. For the present follow-up study, patients who underwent cognitive screening at their 3-months assessment, were re-invited by telephone call for a re-assessment approximately 1 year after hospital discharge.

Procedure

Patients attended the long-COVID clinic at the Bispebjerg Hospital or the Psychiatric Centre Copenhagen, Rigshospitalet, for a 1-year follow-up assessment of objective (performance-based) and subjective (self-reported) cognitive functions, mood symptoms, quality of life and work function (duration of approximately 1 hour).

Materials

Cognitive function was assessed with the Screen for Cognitive Impairment in Psychiatry Danish Version (SCIP-D) which consists of five subtests: (1) verbal learning (VLT-I), (2) working memory (WMT), (3) verbal fluency (VFT), (4) delayed memory (VLT-D) and (5) processing speed (PST) (Jensen et al., 2015; Purdon, 2005) and Trail Making Test- Part B (TMT-B) (TMT-B; Army Battery, 1944). The SCIP-D exists in 3 parallel forms for repeated testing, and 2 alternate versions were used at the 3-month and 1-year assessments. In addition, subjective cognitive functions were assessed with the Cognitive Failures Questionnaire (CFQ), a self-report inventory comprised of 25 items divided in 3 dimensions *perception, memory,* and *motor function*. Items are scored on a 5-point Likert scale (i.e., 0= "never" to 4= "very often") (Broadbent et al, 1982).

Work functioning was assessed for patients who were currently employed with the Work Productivity and Activity Impairment Questionnaire (WPAI; Reilly et al, 1993), a 6-item self-report questionnaire assessing absenteeism, presenteeism, and activity impairments due to health problems in the past 7 days (e.g., "how many hours did you miss from work because of your health problems") (WPAI; Reilly et al, 1993). Quality of Life was assessed with the EQ-5D-5L quality of life questionnaire which is comprised of 5 dimensions: self-care, usual activities, pain/discomfort, mobility, and anxiety/depression. (EQ5D; Lloyd and Pickard, 2019). Additionally, the EQ-5D-5L scale "EQ VAS" was included to assess self-rated health. Items were scored on a 5-point Likert scale (EQ5D; Lloyd and Pickard, 2019). Depressive symptoms were rated with the Hamilton Depression Rating scale 17-items (HDRS-17) (Hamilton, 1960).

Statistical analysis

All statistical tests were conducted using IBM SPSS statistics 25 for windows (IBM Corporation, Armonk, New York) with a significance level of $\alpha = 0.05$ (two-tailed). Prior to statistical analyses relevant assumptions were tested. Regarding normality, appropriate analyses (parametric and non-parametric) tests were used accordingly for normally and non-normally distributed data.

Question (I): What is the frequency, pattern, and severity of cognitive impairments 1 year after hospital discharge?

This research question was examined with two complementary approaches: by comparing patients' cognitive performance at their 1-year assessment (A) to their *individual expected* performance calculated with the regression based formulas based on their age, sex, years of education and the normative (expected) cognitive change with repeated testing (i.e., expected performance considering learning effects with repeated testing, as they had been tested previously, 3 months after hospital discharge) (Supplementary Table 1) and (B) to the cognitive performance of an age-, gender- and education-matched sample of 55 health controls (HC) from a pre-established normative data set following repeated testing (Ott et al., 2021).

In approach (A), regression-based formulas were applied for prediction of each patients *expected* SCIP test scores based on their age, sex, and years of education following repeated testing (Ott et al., 2021). The regression-based formula allows calculation of demographically corrected normative scores, applicable at an individual level (Duff, 2012). This enables precise estimation for each patient of whether their cognition scores deviate or align with the expected scores of a person with matched demographic characteristics. Reliable change indexes (RCI) provide standardized scores for the deviation of the observed scores from the predicted scores, calculated as (observed score – predicted score)/SEE, with SEE reflecting the standard error of the estimate for the regression equation (Attix et al., 2009). These regression-based models have previously been used to determine demographically adjusted norms and normative cognitive change over 1 year (Ott et al., 2021).

The frequency of clinically relevant 'global cognitive impairment' was based on a cut-off score defined as performance $\geq$1 standard deviations (SD) under the *expected* SCIP-D total score, whereas 'selective cognitive impairment' was defined as performance $\geq$ 1SD under the *expected* scores on $\geq$ 2 individual tests in the SCIP-D or TMT-B (Ott et al., 2021) (approach A). The same cut-offs for global and selective impairments were applied when estimating the frequency of clinically relevant cognitive impairments relative to the matched HC sample (approach B). These cut-offs for clinically relevant cognitive impairments were determined based on previous recommendations (Ott et al., 2021; Miskowiak et al., 2018).

Accordingly, the *pattern* of cognitive impairments was explored through comparisons between: (A) patients' actual scores on SCIP-D and TMT-B at the 1-year assessment and their *expected* scores, using independent samples t-tests. For the TMT-B, normative change scores are not available. We therefore compared patients TMT-B scores with the normative cross-sectional TMT-B norms, based on our observation that TMT-B scores show no signs of learning effects

with repeated testing in a large sample of HC ($n = 141$) from our ongoing cohort study (Kessing et al., 2017) over a period of 16 months (change, mean ± SD: 2.9 ± 13.4). Regarding (B), comparisons were made between patients' SCIP-D scores after 1 year and those of the demographically matched HC group (TMT-B data not available for the HC group).

For normally and non-normally distributed data, independent samples t-tests and Mann-Whitney U tests were conducted, respectively. Severity of cognitive impairments (relative to expected performance [approach (A)] and cognitive performance in HC [approach (B)], respectively) was determined based on effect sizes for significant differences. For normally distributed data, Cohen's d effect sizes were estimated. For non-normally distributed data, effect sizes *r* were estimated (r = Z-score / $\sqrt{N}$) (Fritz et al., 2012). Due to unequal sample sizes between patient- and the HC group, severity of cognitive impairments relative to cognitive performance in the HC group, was estimated with Hedges' g.

Question (II): Does cognition improve from 3 months to 1 year after hospitalisation?

This question was explored using the expected *change norms* based on participants' age and baseline scores (Ott et al., 2021). To explore whether proportions of patients with global or selective cognitive impairment at the 1-year assessment were significantly different from 3 months post-discharge, we used non-parametric McNemar's tests for paired nominal data.

In addition, we analysed differences between patients' *actual* change and *expected* change SCIP-D scores between the two assessments using paired sample t-tests, in line with approach (A). Further, we compared patients' SCIP-D change scores between 3 months and 1 year with change scores in the HC group using independent sample t-tests (consistent with approach [B]). Since TMT-B data was not available for HC but is stable over time (Kessing et al., 2017), we analysed patients' change in TMT-B through paired sample t-tests

Question (III): Are cognitive impairments associated with functioning and quality of life?

This was investigated with Pearson's correlations or Spearman's rho for normally and non-normally distributed data, respectively. The deviation from expected scores using the RCI for patients' SCIP-D total scores was applied as a measure in the analyses of associations between objective cognitive function and subjective cognitive complaints, quality of life, mood symptoms and work function.

Question (IV): Are cognitive impairments 3 months after hospitalisation related to mood symptoms after 1 year?

This question was analysed with Pearson correlation analysis. SCIP Total score at 3-months was used as a measure investigating the association with depressive symptoms at 1-year as measured by Hamilton Depression Rating Scale (HDRS-17).

Results

Participants

Following hospitalisation for COVID-19 at Bispebjerg Hospital, 70 % of patients ($n = 83$) were offered follow-up at two-time points; after 3 months and 1 year. Of those offered participation in the study, 86 % accepted ($n = 71$) (See Miskowiak et al., 2021). Fig. 1 illustrates the recruitment process (See Appendix A). For the 3 months follow-up, 29 patients took part ($n = 29$). The results of the 3 months cognition assessments have previously been published (Miskowiak et al., 2021). For the 1-year (mean ± SD: 11 ± 2 months) follow-up, we reassessed 25 (86%) of these patients. Of the 4 patients lost to follow-up, 1 had moved abroad while the other 3 were unreachable by telephone. Importantly, these 4 patients did not differ significantly from the remaining patients on the demographic variables age and gender (*p-levels* > .09). Clinical and demographical characteristics of the resulting sample ($n = 25$) are displayed in Table 1.

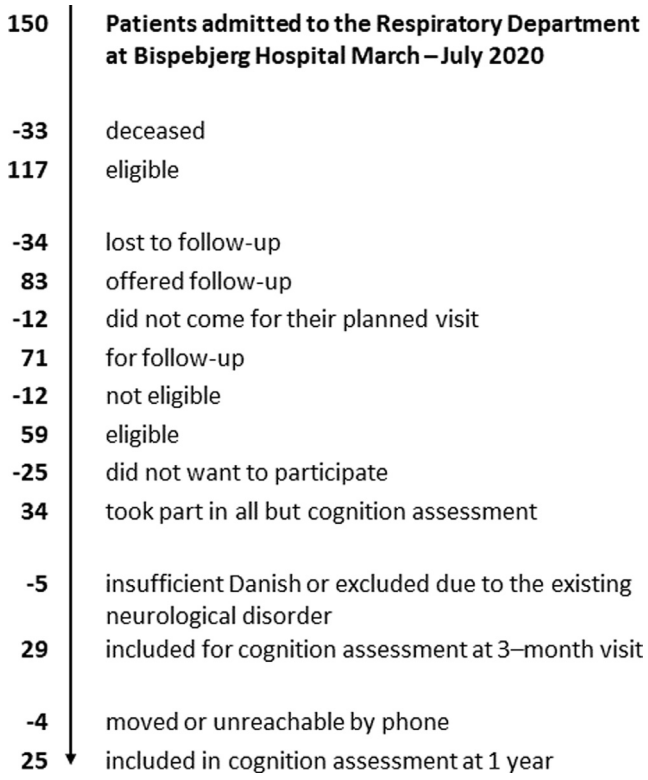

Fig. 1 Flow Chart for recruitment of patients in post-COVID cognition assessments.

Question (I): What is the frequency, pattern, and severity of cognitive impairments 1 year after hospital discharge?

In total, 14 (56%) patients fulfilled the criterion for clinically relevant cognitive impairments compared with their expected performance based on their individual age, education level and gender; 12 (48 %) patients fulfilled the criterion for global impairment, and 2 (8%) patients as selectively impaired, while 11 (44%) were cognitively normal. In comparison with the HC sample, 12 (48%) patients were identified as cognitively impaired; 10 (40%) with global impairments and 2 (8%) with selective impairment, while 13 (52%) were cognitively normal. Cognition data from patients, expected scores and HC is displayed in Table 2 and Fig. 2.

Comparison between patients' actual and expected scores based on the age, gender and education revealed that on average, patients displayed pronounced global cognitive impairment on the SCIP with a large effect size (SCIP Total: t= -3.09, df= 27.42, $p = 0.002$, Cohen's d=-0.87). Large effect size was observed on the working memory test (t= -3.37, df= 25.94, $p = 0.002$, Cohen's d= -0.91). Moderate to large impairments were observed in verbal learning test -immediate (t= -2.67, df= 25.93, $p = 0.008$, Cohen's d= -0.75), verbal fluency test (t= -2.48, df= 25.25, $p = 0.015$, Cohen's d= -0.70), and psychomotor speed test (t= -2.15, df= 30.73, $p = 0.020$, Cohen's d= -0.61). In contrast, a non-significant trend was observed on the trail mak-

Table 1 Demographic and clinical characteristic variables of patients at the 11-months follow-up assessment after hospitalisation with COVID-19 and demographic characteristics of the matched healthy controls (HC).

	Patients ($n = 25$)	Healthy controls ($n = 55$)	*P*-value
Demographics			
Age (years), mean (SD)	56 (10.7)	56.7 (5.2)	.91
Sex, no. Females (%)	12 (48)	25 (46)	.83
Years of education, mean (SD)	14.84 (3.8)	14 (2.7)	.27
Work status, no. employed (%)[a]	12 (48)		
Ethnicity, no. Caucasian (%)	19 (75)		
Clinical Characteristics			
EQ-5D-5L Quality of Life Questionnaire			
Quality of Life Questionnaire total[b]	9.1 (2.6)		
Movement[c]	1.6 (0.9)		
Personal care[d]	1.1 (0.3)		
Usual activity[e]	1.8 (0.6)		
Pain[f]	2.6 (0.9)		
Anxiety/Depression[g]	1.7 (1.1)		
EQ-VAS health[h]	70 (17.1)		
CFQ total, mean (SD)[i]	67 (14.8)		
Hamilton Depression Rating Scale[j]	3.0 (4.2)		
Work productivity and activity impairment			
Percent overall work impairment due to health[k]	20.0 [0.0, 100.0]		
Percent work time missed due to health (absenteeism)	0.0 [0.0, 100.0]		
Percent impairment while working due to health (presenteeism)	15.0 [0.0, 100.0]		
Percent activity impairment due to health[l]	20.0 [0.0, 90.0]		

Data is presented as mean (SD) or number (percentage) for demographics, clinical characteristics, and quality of life data. Work Productivity and Activity Impairment data is reported as median [minimum, maximum].
Missing data for $n = 7$[a,b,h,j,l], Missing data for $n = 9$ [c,d,e,f,g], Missing data for $n = 2$[i]; Missing data for $n = 1$[k]

Table 2 Objective and subjective cognition data from patients and a matched control group as well as the expected scores based on patients age, sex, and education.

	Patients ($n = 25$)	Expected scores based on age, sex, and education	Healthy controls ($n = 55$)	*P*-value all patients actual vs. Expected	*P*-value all patients vs. Healthy controls
SCIP total score, mean (SD)	69.0 (14.5)	78.3 (4)	77.3 (8.4)	.002	.012
VLT-L, mean (SD)	21.2 (4.4)	23.7 (0.9)	23.4 (2.4)	.008	.032
WMT, mean (SD)	18.2 (2.8)	20.1 (0.6)	19.8 (2.9)	.002	.007
VFT, mean (SD)	14 (5.6)	16.8 (0.9)	16.2 (4.5)	.015	.065
VLT-D, mean (SD)	6.5 (2.8)	7.7 (0.4)	7.8 (1.6)	.052	.044
PST, mean (SD)	9.0 (3.0)	10.4 (1.1)	10.2 (1.8)	.020	.076
TMT-B, mean (SD)	94.3 (42.1)	78.0 (16.2)		.090	
CFQ, total mean (SD)	67 (14.8)				

Data is presented as mean (SD) or number (percentage). CFQ data was only available for 23 of the 25 patients; SCIP, Screen for Cognitive Impairment in Psychiatry; SD, standard deviation; VLT-L, verbal learning test-learning; WMT, working memory test; VFT, verbal fluency test; VLT-D, verbal learning test-delayed recall; PST, psychomotor speed test; TMT-B, Trail Making Test B; CFQ, Cognitive Failures Questionnaire.

ing test B (t= 1.73, df= 28.40, $p = 0.09$, Cohen's d= 0.51) and verbal learning test -delayed (t= -2.04, df= 25.02, $p = 0.052$, Cohen's d= -0.58) (see Fig. 3).

Comparisons of patients with the matched HC group revealed similar results. Patients exhibited global cognitive impairments with a large effect size (SCIP total: t= 2.67, df= 31.4, $p = 0.012$, Hedges' g= 0.78). Moderate to large effect sizes were observed in verbal learning test - immediate (t= 2.25, df = 30.73, $p = 0.032$, Hedges' g= 0.67), WMT (U= 814,00 $p = 0.007$, r= -0.30) and -delayed (t= 2.10, df= 31.30, $p = 0.044$, Hedges' g= 0.62). Non-significant trends toward group differences were found for psychomotor speed and verbal fluency (PST: t= 1.84, df= 32.24, $p = 0.076$, Hedges' g= 0.53; VFT: t= 1.87, df = 78, $p = 0.065$, Hedges' g= 0.45). The pattern of cognitive deficits across groups is displayed in Fig. 3.

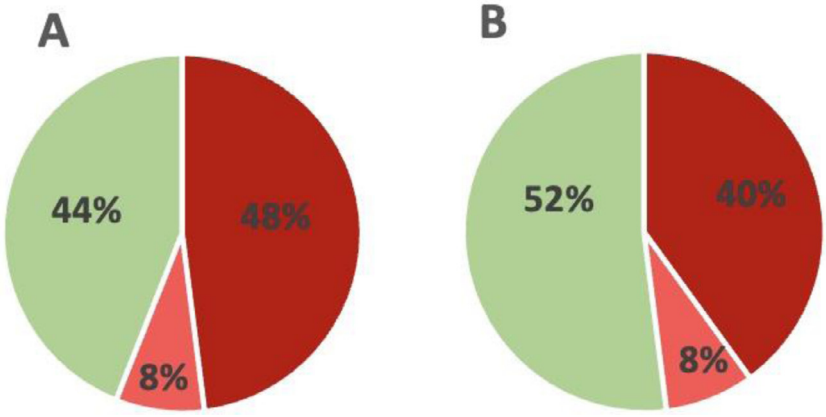

Fig. 2 Frequency of clinically significant cognitive impairments. (A) Proportion of patients with clinically relevant global or selective cognitive impairments using a cut-off for global impairment (dark red) defined as SCIP Total scores ≥1 below demographically adjusted norms and – for selective impairments (light red) – performance ≥1 SD below the demographically adjusted norms, on ≥2 individual tests. (B) Finally, proportion of patients with clinically relevant global or selective cognitive impairments using a cut-off for global impairment defined as SCIP Total scores ≥1 below 55 age- and education matched healthy controls (HC) following repeated testing and – for selective impairments – performance ≥1 SD below HC ≥2 individual tests. *Dark red = global cognitive impairment; light red= selective cognitive impairment; green = cognitively normal.*

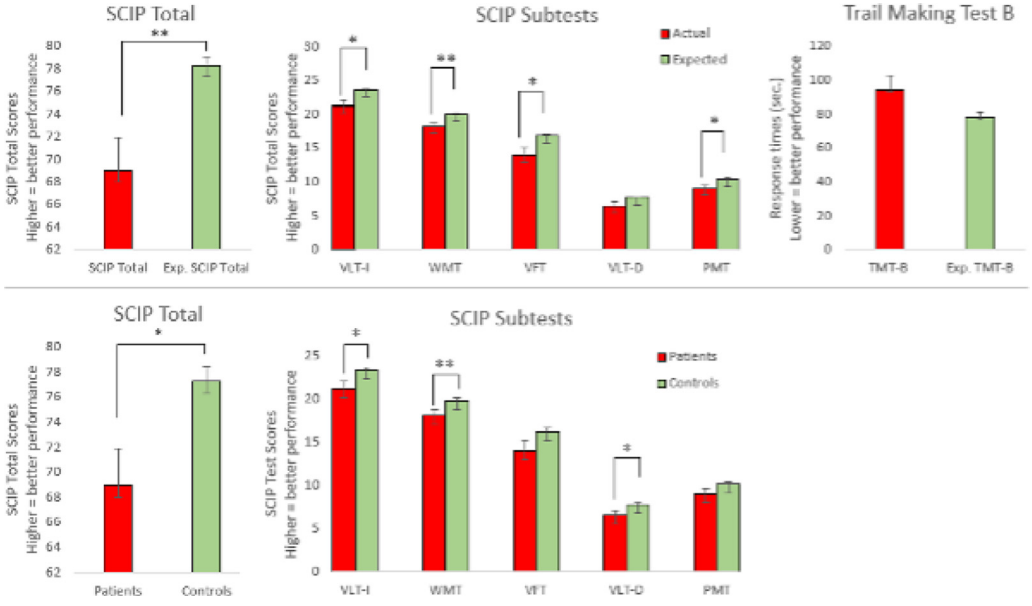

Fig. 3 Pattern and severity of cognitive impairments in patients 1 year after COVID-19 hospitalisation. Top: cognitive impairments in patients (red) in comparison with expected normative scores adjusted for age, sex and education (green). Bottom: cognitive impairments in patients (red) in comparison with scores of 55 healthy demographically matched controls following repeated testing. Graphs represent the mean whereas error bars represent the standard error of the mean. *= $p < 0.05$ (two-tailed); **= $p < 0.01$ (two-tailed); *** = $p < 0.001$ (two-tailed).

Question (II): Does cognition improve from 3 months to 1 year after hospitalisation?

There was no significant difference in the proportion of patients with global or selective cognitive impairment between the 3-months assessment (32% and 24 %, respectively) and the 1 year assessment (48% and 8%, respectively) (p-values ≥ 0.22 and ≥ 0.13. respectively). Cognitive change in individual patients from the 3-months to 11-months assessments is illustrated in Fig. 4.

There were also no significant differences between patients' test scores at 3 months and 1 year on the SCIP-D or TMT-B (p-vales ≥ 0.19). However, when adjusting the analyses for the normative change due to learning effects with repeated testing, patients showed a *lack of the expected increase* over time in SCIP-D total scores (mean ± SD, actual change: -0.2 ± 7.4; expected change: 9.1 ± 11.8; $t(24)$= -3.49, $p = 0.002$, Cohen's $d = 0.94$) and on the five SCIP-D subtests (p-values ≤ 0.05) but not for TMT-B ($p = 0.06$).

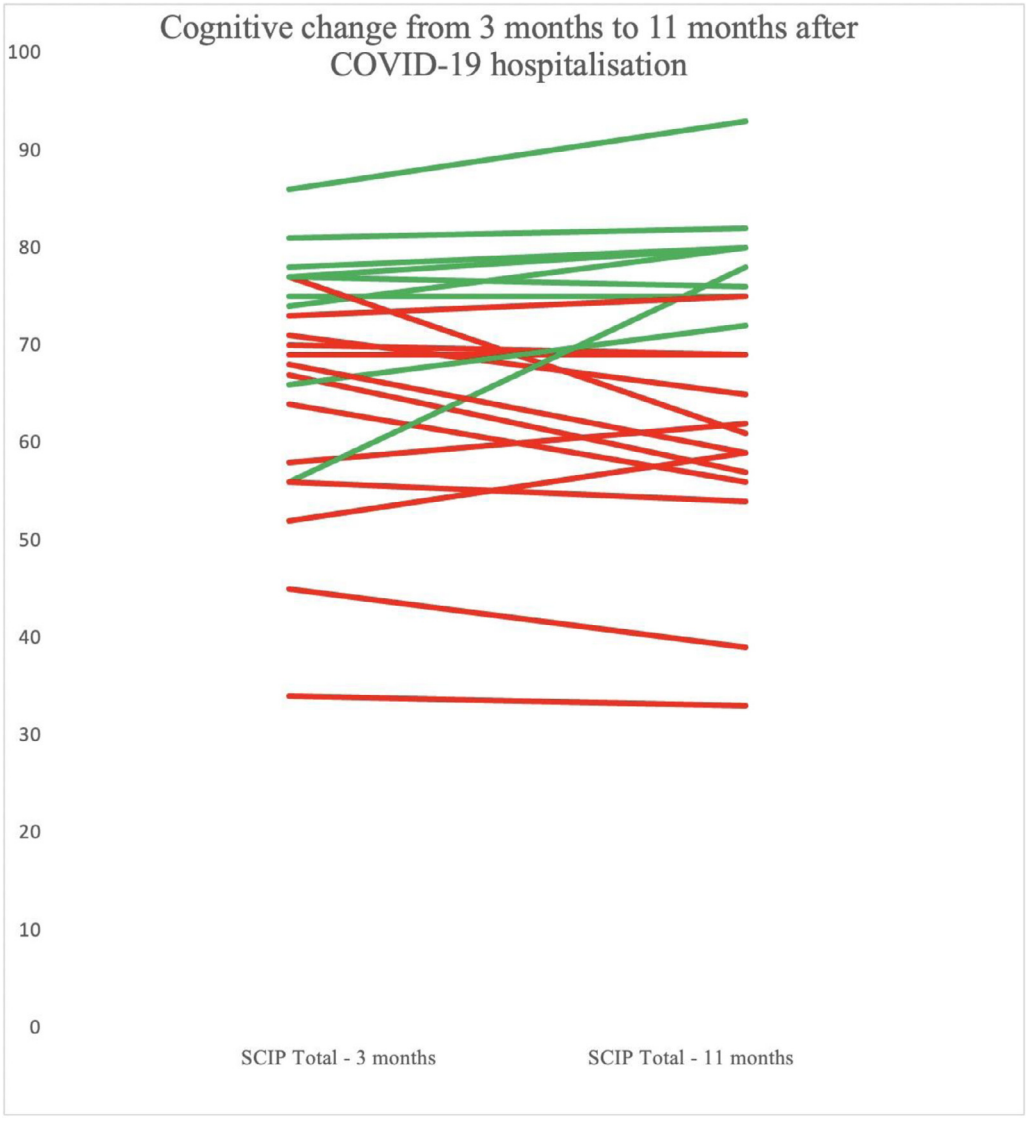

Fig. 4 The trajectory of cognitive change from 3 months to 1 year in patients hospitalised with COVID-19. SCIP-D Total scores measured at the 3-months (*M*= 69.2, *SD*= 13.2) and 11-months (*M*= 69.0, *SD*= 14.5) assessments, respectively. *Dark red*= *cognitive impairment; green* = *cognitively normal*.

Comparison with in the HC group (approach [B]) also revealed less improvement in patients in SCIP-D total scores (mean ± SD, patients: -0.20 ± 7.4; HC: 3.0 ± 6.0; $t = 2.02$, df = 39.1, $p = 0.046$, Hedges' $g = 0.49$) but not on the individual SCIP-D subtests (p-values ≥ 0.09).

Question (III): Are cognitive impairments associated with functioning and quality of life?

Global cognitive impairments correlated moderately with subjective cognitive complaints (Pearson's correlation: r = -0.61 $p < .01$). Regarding quality-of-life measurements, global cognitive impairments revealed a moderate correlation with EQ-5D-5L Quality of Life Questionnaire Total (Pearson's correlation: r = -0.56, $p = 0.02$). Additionally, more global cognitive impairment correlated moderately with more anxiety and depression (EQ-5D-5L subscale 'anxiety and depression', Pearson's correlation: r = -0.66, $p = 0.01$), poorer health (Pearson's correlation: r = -0.54, $p = 0.02$), and more pain and discomfort (Pearson's correlation: r = -0.50, $p = 0.05$) measured with the EQ-5D-5L. In addition, global cognitive impairment correlated with greater subsyndromal depression symptoms, measured with HDRS-17 (Pearson's correlation; r = -0.54, $p = 0.02$). Global cognitive impairment also correlated strongly with impairments in several aspects of work function measured with the WPAI, including work productivity loss' (i.e., overall work impairment; Spearman's Rho; r = -0.75, $p = 0.01$), 'presenteeism' (i.e., impairment at work; Spearman's Rho'; r = -0.70, $p = 0.01$), and 'activity impairment' (Spearman's Rho; r = -0.69, $p < 0.01$). In contrast, no relation was found between global cognitive impairment and the WPAI 'absenteeism' (i.e., work time missed) ($p \geq .46$).

Question (IV): Are cognitive impairments 3 months after hospitalisation related to mood symptoms after 1 year?

A moderate correlation was found between cognitive impairments 3 months after hospital discharge and the

severity of depressive symptoms after 1 year (Pearson's correlation; $r = -0.49$, $p = 0.04$).

Discussion

In this longitudinal study of patients hospitalised with COVID-19, we examined the frequency and pattern of cognitive impairments and associations with quality of life and work functioning 1 year after hospital discharge (mean ± SD; 11 ± 2 months) and the cognitive *trajectory* from patients' prior 3-months assessments (Miskowiak et al., 2021). The percentages of patients with *clinically relevant* cognitive impairments after 1 year were 48 % and 56 % when compared to a matched healthy control group and demographically adjusted norms, respectively. This did not differ significantly from the frequency of impairments observed 3 months after hospitalisation. Regarding the pattern of deficits, verbal learning and executive function were most affected, with moderate to large effect sizes for deficits in these domains. These objective cognitive impairments correlated strongly with overall work impairment, presenteeism, and activity impairment. In addition, objective cognitive impairments correlated moderately with subjective cognitive difficulties and with poorer quality of life, including poor health, pain, anxiety and depression. Finally, cognitive impairments 3 months after hospitalisation correlated moderately with depressive symptoms 1 year after hospitalisation.

The observed trajectory of cognitive functions from 3 months to 1 year after hospitalisation with COVID-19 indicates that patients with impaired cognition 3 months after hospitalisation do not improve after 1 year, while patients with no impairments after 3 months remain cognitively normal. This is consistent with meta-analytic evidence suggesting patients' cognitive impairments after COVID-19 persist over time (Ceban et al., 2022). Our findings corroborate with 3 longitudinal studies that identified cognitive impairments both 6 (Poletti et al., 2021) and 12 months (Méndez et al., 2022; Ferrucci et al., 2022) after COVID-19 hospitalisation, with most pronounced impairments within verbal learning, memory and executive function (Méndez et al., 2022). While Ferrucci and colleagues observed improvement in verbal memory, attention, and processing speed, cognitive functions were still affected after 1 year, with processing speed, visuospatial and verbal memory being most affected (Ferrucci et al., 2022). No study has yet investigated whether cognitive COVID persists beyond 1 year. However, longer-term follow-up assessment of patients with other respiratory illnesses, including SARS-CoV-1 and MERS, indicates that neurocognitive and functional impairments may last up to 5 years after hospitalisation with these diseases, particularly in severely ill patients with acute respiratory distress syndrome (ARDS) (O'Sullivan, 2021; Sasannejad et al., 2019). Nevertheless, studies with longer follow-up times are needed to determine the long-term trajectory of cognitive deficits after COVID-19.

The moderate to strong associations between cognitive impairments and daily functioning, quality of life and low mood 1 year after hospitalisation with COVID-19 is noteworthy. This finding is in keeping with the observation by Mendez and colleagues in a larger sample of patients ($n = 171$) that cognitive impairments, subjective cognitive complaints, psychiatric morbidity, and poorer quality of life are prevalent 1 year after hospitalisation with COVID-19 (Méndez et al., 2022). The lack of cognitive improvements from 3 months to 1 year is also consistent with the observations that patients often do not return to previous levels of work capacity even 1 year after COVID-19 hospitalisation (Davis et al., 2021; Frontera et al., 2021). Importantly, we showed here for the first time that cognitive impairments are strongly associated with reduced work capacity, and moderately associated with self-reported cognitive difficulties in daily life, poorer quality of life, and elevated mood symptoms 1 year after hospital discharge. In particular, the moderate correlation between objectively measured and subjective self-reported cognitive impairment suggests that patients' insight into their cognitive status was adequate. This contrasts with the generally poor correlation between subjective and objective cognition in patients with mood disorders (e.g., Petersen et al., 2019). Cognitive screening with easy-to-administer self-report measures may thus be adequate for patients in long-COVID clinics.

Interestingly, a longitudinal study of 1,276 hospitalised patients in China revealed that while most patients had returned to work within 12 months after hospitalisation with COVID-19 (88%), a substantial subset (26 %) was battling with unchanged levels of mood symptoms from 6 to 12 months after their hospital discharge (L. Huang et al., 2021). It is likely that patients' return to work despite lingering symptoms will aid their recovery and help them regain their cognitive abilities and daily functioning after COVID-19. Indeed, environmental stimulation seems crucial for enhancing and preserving cognitive function (Shaffer, 2016), possibly through a positive impact on patients' neuroplasticity. However, work demands should not exceed people's cognitive capacity, because this would likely result in stress and poor mental health. In this regard, cognitive screening after COVID-19 hospitalisation and implementation of appropriate support for patients with identified cognitive impairments may be clinically useful.

Depressive symptoms were found in a previous study to be the main predictor of impaired cognitive performance 6 months after hospitalisation with COVID-19 (Poletti et al., 2021). Our finding that cognitive impairments 3 months after hospitalisation were moderately associated with subsequent depressive symptomatology after 1 year provides preliminary evidence that the opposite may also be the case. While the sample size was too small for multiple regression analyses with covariation for other potential contributing factors, this association provides preliminary evidence for a potential role of cognitive COVID in the development of depressive symptoms. Cognitive impairments and mood symptoms are thus likely to have a bi-directional relation; In a mutually reinforcing cycle, cognitive impairments may exacerbate depression and anxiety symptoms due to difficulties overcoming cognitive challenges in daily life and work functioning and, thereby, result in poorer quality of life, stress, and mood symptoms. On the other hand, mood and anxiety symptoms may also exacerbate cognitive impairment and functional disability. This highlights a need to screen for and target both cognitive impairment and mood symptoms after severe COVID-19 illness. Regarding cogni-

tive screening, the finding that *objectively* measured cognitive impairment scaled with *subjectively* self-reported cognitive difficulties indicates that patients may have accurate insight into their cognitive status. This supports the use of the CFQ or similar easy-to-administer self-report measures to screen for cognitive difficulties after COVID-19.

While the functional implications of cognitive impairments after COVID-19 are evident, the neurobiological origins of these long-term impairments remain unclear and are likely multifactorial (Baldini et al., 2021; Mazza et al., 2021; Moonis et al., 2020; Scardua Silva et al., 2021). In our 3-months assessment study of these patients, we had observed that the degree of cognitive impairment was related to higher d-dimer levels during acute illness and residual pulmonary dysfunction. This suggests that reduced oxygen delivery to the brain and possible thrombosis or coagulation may play a role in patients' cognitive impairments (Miskowiak et al., 2021). In particular, the hippocampus - an essential brain structure for memory function- is highly susceptible to hypoxia-related injury, suggesting that cerebral oxygen starvation during acute illness may contribute to these patients' long-term verbal learning and memory difficulties.

The careful longitudinal evaluations over 1 year of cognition, functioning and quality of life and the well-defined sample of patients hospitalized with COVID-19 were strengths of the study (Miskowiak et al., 2021). A key limitation, however, was the small sample size ($n = 25$) and consequent low statistical power, which limited our ability to conduct extensive and thorough statistical analyses of the associations between variables. Nevertheless, we were able to observe robust group differences in cognitive functions with moderate to large effect sizes, similar to a prior larger study (Méndez et al., 2022) as well as moderate to strong associations between cognitive impairments and work difficulties, mood symptoms and quality of life. It is possible that they experienced no cognitive-COVID, indicating that our findings may only be generalised to patients with lingering symptoms. However, the reasons for declining were often exhaustion and lack of energy for cognitive testing, which would speak against a sampling bias. Further, the lack of control group of patients with a different respiratory illness prevented insight into whether the observed cognitive impairments were specific to COVID-19 illness. Finally, SCIP-D is a brief cognition screener and may not replace comprehensive neuropsychological evaluation. Nevertheless, the SCIP-D is short, sensitive and feasible, rendering complete longitudinal datasets for all included participants.

Conclusion

In conclusion, our prospective follow-up study revealed that 48-56 % of patients suffer from *clinically relevant* cognitive impairments 1 year after hospitalisation with COVID-19, which were of a moderate to large effect size for the global cognition measure, verbal learning and executive function. Longitudinal analyses showed stability of these impairments from 3 months to 1 year after hospitalisation. Further, the cognitive impairments after 1 year were moderately to strongly associated with poorer quality of life, more mood symptoms and greater work impairments. The observed association between cognitive impairments after 3 months and severity of depressive symptoms 1 year after hospitalisation provides preliminary evidence for a possible role of cognitive status in mental health outcomes after hospitalisation with COVID-19. Based on these findings, we suggest that there is a need to assess and address cognitive difficulties, mood symptoms and functional impairments after severe COVID-19 illness.

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Contributors

KWM and SJ defined the aim and hypotheses of this report. KWM, AEJ, SMS, DP and SJ were involved in conducting the study and assessing the patients under supervision of CMP. LF and AEJ conducted the statistical analyses under supervision of KWM. KWM and LF wrote the first draft. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest in relation to the current manuscript. Outside of the present work, KWM reports having received consultancy fees from Janssen-Cilag and Lundbeck; JR reports having received consultancy fees from Novo Nordisk, Boehringer-Ingelheim and Astra-Zeneca; CMP reports having received consultancy honararia and unrestricted grants from Astra Zeneca, Novartis, Sanofi, GSK, TEVA, ALK, Chiesi and Pharmaxis in the past three years; SJ, DP and SMS report no conflicts of interest outside of the present work.

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