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Original article

Cognitive and psychological recovery patterns across different care pathways 12 months after hospitalization for COVID-19: A multicenter cohort study (CO-FLOW)

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Background: The comparison of recovery patterns for different care pathways following COVID-19 is necessary for optimizing rehabilitation strategies.
Objectives: To evaluate cognitive and psychological outcomes across different care pathways up to 12 months after hospitalization for COVID-19.
Methods: CO-FLOW is an ongoing multicenter prospective cohort study with assessments at 3, 6, and 12 months after hospitalization for COVID-19. The main outcomes are cognitive deficits (Montreal Cognitive Assessment, score <26), cognitive failure (Cognitive Failure Questionnaire, score >43), posttraumatic stress disorder (PTSD; Impact of Event Scale-Revised, score ≥33), and anxiety and depression (Hospital Anxiety and Depression Scale, subscale score ≥11).
Results: In total, data from 617 participants were analyzed. Mean age was 59.7 (SD 11.4) years and 188 (31%) were female. Significant recovery occurred within the first 6 months post-discharge ($p \leq 0.001$). Cognitive deficits persisted in 21% (101/474), and psychological problems in 15% (74/482) of people at 12 months. Significantly improved cognition scores were reported for people who did not receive rehabilitation ('No-rehab'; 124/617, 20%; mean difference, MD 2.32, 95% CI 1.47 to 3.17; p<0.001), those who received community-based rehabilitation ('Com-rehab'; 327/617, 53%; MD 1.27, 95% CI 0.77 to 1.78; p<0.001), and those who received medical rehabilitation ('Med-rehab'; 86/617, 14%; MD 1.63, 95% CI 0.17 to 3.10; p = 0.029). Med-rehab participants experienced more cognitive failure from 3 to 6 months (MD 4.24, 95% 1.63 to 6.84; p = 0.001). Com-rehab showed recovery for PTSD (MD −2.43, 95% −3.50 to −1.37; p<0.001), anxiety (MD −0.67, 95% −1.02 to −0.32; p<0.001), and depression (MD −0.60, 95% −0.96 to −0.25; p<0.001), but symptoms persisted at 12 months.
Conclusions: Survivors of COVID-19 showed cognitive and psychological recovery, especially within the first 6 months after hospitalization. Most persistent problems were related to cognitive functioning at 12 months. Recovery differed rehabilitation settings. Additional cognitive or psychological support might be warranted in people who medical or community-based rehabilitation.

Abbreviations: BMI, Body mass index; CFQ, Cognitive failure questionnaire; CO-FLOW, COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system; Com-rehab, Community-based rehabilitation; COVID-19, Coronavirus disease 2019; EPR, Electronic patient records; GEE, Generalized estimating equations; HADS, Hospital anxiety and depression scale; HADS-A, Hospital anxiety and depression scale – anxiety subscale; HADS-D, Hospital anxiety and depression scale – depression subscale; ICU, Intensive care unit; IES-R, Impact of event scale-revised; iMCQ, iMTA Medical Cost Questionnaire; IMTA, Institute for Medical Technology Assessment; LOS, Length of stay; MD, Mean difference; Med-rehab, Medical rehabilitation; MoCA, Montreal cognitive assessment; No-rehab, No rehabilitation; PTSD, Posttraumatic stress disorder; SNF, Skilled nursing facilities; SNF-rehab, Skilled nursing rehabilitation

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Introduction

Many cases of coronavirus disease 2019 (COVID-19) involve long-term symptoms [1] and 6 months after hospitalization, 70−89% of people report at least one persistent symptom, and this figure is 49% at 12 months [2–5]. One of the most common symptoms is cognitive dysfunction, manifesting as problems with concentration, memory and brain fog [6–9]. Studies that objectively measure cognitive functioning have reported cognitive deficits in 31−69% of people during, or shortly after, hospitalization [10–13] and in ≥80% of people in rehabilitation settings [14,15]. Cognitive deficits were present in 50−75% of hospitalized survivors in at least one cognitive domain at 6 months [16,17], and in 16% at 12 months [18]. At 12 months after intensive care unit (ICU) discharge, 16% of people experienced self-reported cognitive failure [19].

In addition to cognitive deficits and failure, people with COVID-19 frequently report psychological impairments [7,8,20-22] with 43% of people experiencing posttraumatic stress disorder (PTSD), 46% reporting anxiety, and 30% reporting depression up to 6 months after hospitalization for COVID-19 [4,16,23-25]. Longitudinal studies that follow-up people hospitalized for COVID-19 for 15 months report that up to 10% of people experience PTSD and 26% report anxiety and/or depression [5,18,19,26]. However, there is a lack of large, multicenter, prospective cohort studies comparing recovery across multiple rehabilitation settings [10,14].

At the onset of the COVID-19 pandemic, care pathways were rapidly established without sufficient knowledge of people's clinical and rehabilitation needs, or long-term sequelae. Guidelines about who would need what type of rehabilitation did not yet exist. After hospitalization, most people are discharged home and if they receive community-based rehabilitation, it is usually a monodisciplinary physical therapy. More severely affected, and younger, people are referred for medical rehabilitation while vulnerable people with more comorbidities are referred for skilled nursing facilities (SNF), where they receive multidisciplinary rehabilitation [27].

In the Netherlands, rehabilitation programs are highly tailored to an individual's needs and goals. Rehabilitation intensity and total duration depends on factors such as disease characteristics or personal context, eg, the presence of a care-giver. Rehabilitation has shown to improve cognitive performance in people with acute respiratory distress syndrome and sepsis [28]. Exploring the variations and outcomes among different care pathways for people with COVID-19 is necessary to optimize rehabilitation strategies as variations in post-COVID rehabilitation may lead to different outcomes. Studies of COVID rehabilitation programs have been conducted within specific settings like hospitals and rehabilitation centers [12,14,18] but, to date, long-term outcomes across settings have not been compared.

We hypothesized that people who followed multidisciplinary rehabilitation will have a longer recovery time than those to whom either no rehabilitation, or monodisciplinary rehabilitation, was offered. Therefore, we aimed to evaluate the cognitive (objective and subjective) and psychological recovery patterns among survivors of COVID-19 across multiple care pathways up to 12 months after hospitalization.

Material and methods

Study design and population

The COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system (CO-FLOW) study is an ongoing, multicenter prospective cohort study in which participants are monitored at 3, 6, 12, and 24 months after hospital discharge and at rehabilitation discharge, if applicable, within the Rotterdam-Rijnmond-Delft area of the Netherlands. Eligible participants are people within 6 months after hospitalization for COVID-19 (diagnosed by laboratory or clinical findings), ≥18 years old, and fluent in Dutch or English. The CO-FLOW protocol has been described in detail elsewhere [29].

Here we present interim results from people up to 12 months after hospital discharge with at least one study measurement between July 1, 2020 and June 13, 2022. All participants provided written informed consent before the first study measurement. The Medical Ethics Committee of the Erasmus Medical Center study (MEC-2020−0487) approved this study. The study is registered on the World Health Organization International Clinical Trials Registry Platform (NL8710) and is reported in accordance with the STROBE guidelines.

Procedure

Demographics and clinical characteristics were collected at study visits and from electronic patient records (EPR). Demographics included age, sex, body mass index (BMI), migration background, and pre-COVID educational and employment status. Clinical characteristics included medical history, length of stay (LOS) in hospital, treatment during admission, oxygen support, ICU admission, LOS in ICU, delirium, and thrombosis. Healthcare use was collected via face-to-face interview, EPR, and the iMTA Medical Cost Questionnaire (iMCQ) [30]. Medication use was collected via iMCQ. After being discharged from hospital, participants were grouped according to their care pathway (Supplemental Figure 1):

1) No rehabilitation (No-rehab) group: participants returned home independently and did not receive rehabilitation.
2) Community-based rehabilitation (Com-rehab) group: participants received outpatient rehabilitation to support their recovery to premorbid functional levels; they were usually offered monodisciplinary rehabilitation programs (lasting from weeks to months) of psychotherapy, physical, or occupational therapy
3) In- and outpatient medical rehabilitation (Med-rehab) group: participants received intensive in- or outpatient multidisciplinary rehabilitation to support independence and functional recovery to premorbid levels; the aim of inpatient rehabilitation is to return home. Rehabilitation programs are individualized and person-centered as functional goals determine the type and duration of treatment. The program is guided by a multidisciplinary team and, depending on the individual's care needs, includes a rehabilitation physician, physical, occupational, movement, and speech and language therapists, psychologists, nurses, dieticians, and social workers. Inpatient rehabilitation treatment is often provided 4−5 times per day for approximately 4−6 weeks. Outpatient rehabilitation programs usually last 8−12 weeks. After inpatient rehabilitation, people may continue onto outpatient medical or community-based rehabilitation programs.
4) Inpatient skilled nursing rehabilitation (SNF-rehab) group: participants received moderately intensive inpatient multidisciplinary rehabilitation to support independence and recovery to premorbid functional levels in order to return home. Rehabilitation programs are individualized as the functional goals determine the type and duration of treatment. Rehabilitation programs are guided by a multidisciplinary team that includes an elderly-care physician, therapists (physical, occupational, movement, and speech and language), psychologists, nurses, dieticians, and social workers, as necessary. During inpatient rehabilitation, treatment

is provided up to 5 times a week for 4–8 weeks; afterwards people may follow community-based rehabilitation programs.

Study visits were scheduled at 3, 6, and 12 months and included non-invasive functional tests assessing physical and cognitive abilities. Participants also received questionnaires via email or by post. Data were stored using an electronic data capture system (Castor EDC, Amsterdam, The Netherlands).

Outcome measures

The Montreal Cognitive Assessment (MoCA) is a screening tool that objectively evaluates 8 cognitive domains [31]. The total score ranges from 0 to 30; a score <26 indicates cognitive deficits. A point is added if the patient has participated in education for ≤12 years. The MoCA was administered at the first possible visit with the participant, and subsequently repeated only for those with a score of <26, to follow clinical practice as closely as possible and reduce participant burden at the next study visit. We used a different MoCA version each time.

The Cognitive Failure Questionnaire (CFQ) subjectively assesses the frequency of experienced cognitive failures in everyday life [32,33]. It contains 25 items, each scored using a 5-point Likert scale from 0 (“never”) to 4 (“very often”). The total score ranges from 0 to 100, a score >43 indicates cognitive failure.

Psychological status included PTSD, anxiety, and depression. PTSD was assessed using the Impact of Event Scale-Revised (IES-R) which includes 22 items rated by a 5-point Likert scale from 0 (“not at all”) to 4 (“extremely”) [34,35]. The total score ranges from 0 to 88, and a result ≥33 indicates clinically significant PTSD. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) subscales for anxiety (HADS-A) and depression (HADS-D). Each subscale score ranges from 0 to 21; for either a score ≥11 indicates clinically significant anxiety or depression [36].

Data analysis

Data were analyzed from participants with at least 1 follow-up outcome of interest. Variables are presented as means with standard deviation (SD), medians with interquartile range (IQR), numbers (n) with percentage (%), or estimated means with standard error (SE), as appropriate. We used Generalized Estimating Equations (GEE), with repeated measurements of MoCA, CFQ, IES-R, HADS-A, and HADS-D scores, to assess recovery patterns over time for the full cohort and across care pathways. GEE accounted for within-person correlations using a working correlation matrix between repeated measurements, and included all observed outcomes, despite missing values. We considered the unstructured correlation matrix the best option for our data. We entered visit time (3, 6, and 12 months) as a fixed factor in the GEE for the full cohort. We entered care pathway (No-, Com-, Med-, or SNF-rehab) as a fixed factor, and the interaction of care pathway and visit time (3, 6, and 12 months), and adjusted for age at admission, sex, BMI at admission, pre-COVID employment, and length of hospital stay in the GEE for subgroup analyses. Post-hoc analyses included pairwise comparisons between follow-up visits and care pathways. Only significant results between care pathways are reported.

The main GEE analysis of MoCA data included only participants who scored <26 during their first assessment after hospital discharge or, for some, upon their discharge from inpatient rehabilitation to show recovery over time. MoCA testing was not repeated when a participant scored ≥26. Twenty-two people scored ≥26 (22/86) at their first assessment at inpatient rehabilitation discharge, thus this was re-used as their 3-month outcome. In addition, an exploratory GEE was performed for the full cohort in which scores ≥26 were carried over and used for all future study time points.

We calculated Spearman’s correlations (r; <0.5, mild; 0.5–0.7, moderate; and >0.7, strong) to evaluate associations between the outcomes of interest at 12 months. All statistical tests were 2-sided, and statistical significance was defined as a p-value of <0.05. The Bonferroni correction was applied to group comparisons of baseline characteristics. We used SPSS (version 28, SPSS Inc, Chicago, IL, USA) for the statistical analyses.

Results

Study population

Of the 650 participants enrolled in CO-FLOW, 617 (95%) were analyzed as they had at least 1 study measurement as of June 13, 2022 (Fig. 1). The mean age was 59.7 (11.4) years, 188 (31%) were female, and the median hospital LOS was 12 (6–27) days. Distribution of the care pathways was: No-rehab, 124/617 (20%); Com-rehab, 327/617 (53%); Med-rehab, 86/617 (14%); and SNF-rehab, 80/617 (13%) (Table 1). Median (IQR) inpatient rehabilitation times were: Med-

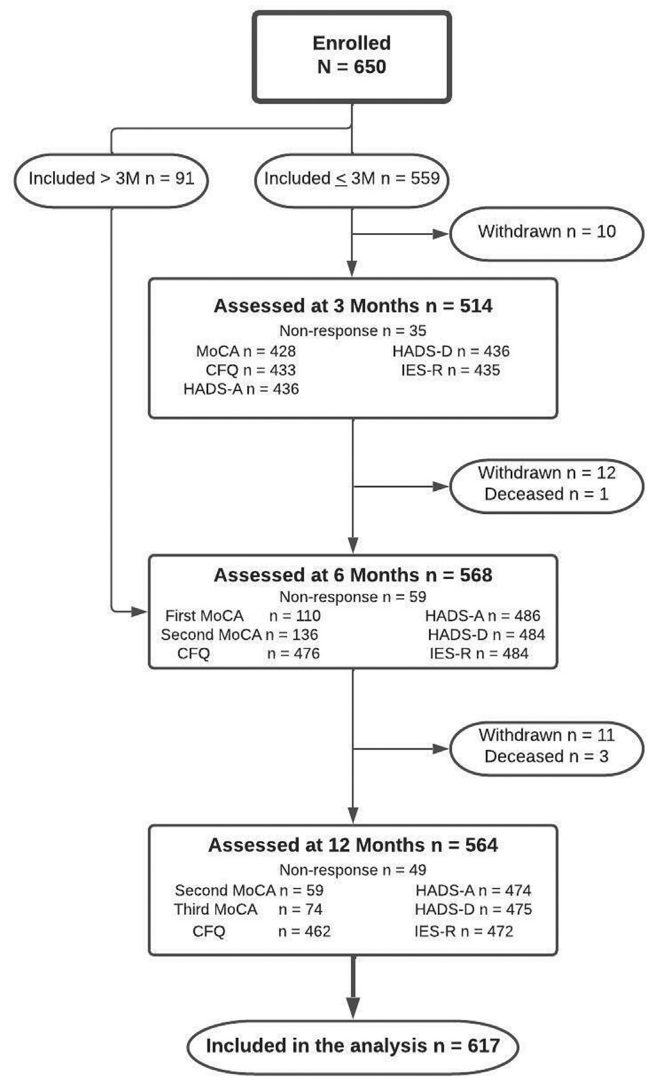

Fig. 1. Flowchart of the CO-FLOW study recruitment and data gathering process. In the current analysis, 617 participants who had at least one outcome of interest were included and were assessed at 3, 6, and 12 months after hospitalization for COVID-19.

>3 M, participants included after 3 months after hospital discharge; ≤3 M, participants included within 3 months of hospital discharge; CFQ, Cognitive Failure Questionnaire; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale, IES-R, Impact of Event Scale-Revised; MoCA, Montreal Cognitive Assessment; M, Months.

Table 1
Demographics and clinical characteristics for 617 people who had been hospitalized for COVID-19. Data were grouped according to care pathway followed after hospital discharge as part of the CO-FLOW study.

	n	Total cohort	No-rehab	Com-rehab	Med-rehab	SNF-rehab	p-value [b]
Number (n)	617	617 (100.0)	124 (20.1)	327 (53.0)	86 (13.9)	80 (13.0)	
Demographics							
Age at admission in years, mean (SD)	617	59.7 (11.4)	58.5 (12.8)	59.4 (11.4)	57.0 (8.2)	66.1 (9.6)	<0.001*
Sex, female	613	188 (31)	30 (24)	117 (36)	19 (22)	22 (28)	0.020
Body mass index (BMI), mean (SD)	559	29.3 (5.3)	28.1 (5.0)	29.1 (5.3)	31.1 (5.3)	29.6 (5.6)	<0.001*
Migration background	608						0.910 [a]
European		442 (73)	86 (71)	238 (74)	62 (72)	56 (71)	
(North) African		23 (4)	5 (4)	16 (5)	1 (1)	1 (1)	
Dutch Caribbean		83 (14)	19 (16)	39 (12)	13 (15)	12 (15)	
Asian		38 (6)	6 (5)	16 (5)	8 (9)	8 (10)	
Turkish		22 (4)	5 (4)	13 (4)	2 (2)	2 (3)	
Pre-COVID educational level	506						0.360
Low		210 (35)	42 (35)	109 (34)	25 (29)	34 (44)	
Middle		213 (35)	40 (33)	110 (34)	35 (41)	28 (36)	
High		183 (30)	39 (32)	103 (32)	25 (29)	16 (21)	
Pre-COVID employment	608						<0.001*
Unemployed		94 (15)	16 (13)	57 (17)	4 (5)	17 (22)	
Employed		364 (60)	73 (60)	189 (59)	73 (86)	29 (37)	
Retirement		150 (25)	32 (26)	77 (24)	8 (10)	33 (42)	
Clinical characteristics							
Comorbidities	617						
≥1 comorbidity		501 (81)	84 (68)	272 (83)	72 (84)	73 (91)	<0.001*
Obesity (BMI ≥30)		234 (38)	29 (23)	122 (37)	52 (61)	31 (39)	<0.001*
Diabetes		120 (19)	21 (17)	65 (20)	13 (15)	21 (26)	0.273
Cardiovascular disease and/or hypertension		240 (39)	35 (28)	126 (39)	35 (41)	44 (55)	0.002
Pulmonary disease		152 (25)	19 (15)	89 (27)	21 (24)	23 (29)	0.052
Renal disease		58 (9)	11 (9)	33 (10)	5 (6)	9 (11)	0.606
Gastrointestinal disease		30 (5)	6 (5)	16 (5)	7 (8)	1 (1)	0.224
Neurological disease		65 (11)	9 (7)	30 (9)	8 (9)	18 (23)	0.003
Malignancy		68 (11)	9 (7)	38 (12)	9 (11)	12 (15)	0.360
Autoimmune and/or inflammatory disease		66 (11)	12 (10)	33 (10)	8 (9)	13 (16)	0.392
Mental disorder		29 (5)	3 (2)	16 (5)	6 (7)	4 (5)	0.445
Length of stay hospital in days	617						
mean (SD)		19.4 (20.1)	8.8 (7.8)	12.6 (11.5)	46.6 (24.0)	34.4 (21.9)	<0.001*
median (IQR)		12.0 (6.0–27.0)	7.0 (4.0–10.0)	9.0 (5.0–16.0)	44.0 (31.5–55.3)	29.0 (20.3–46.8)	
Treatment	617						0.109 [a]
No treatment		134 (22)	35 (28)	61 (19)	17 (20)	21 (26)	
(Hydroxy)chloroquine		12 (2)	2 (2)	3 (1)	7 (8)	NA	
Antivirals		93 (15)	28 (23)	58 (18)	5 (6)	2 (3)	
Steroids		434 (70)	80 (65)	248 (76)	51 (59)	55 (69)	
Anti-inflammatories		74 (12)	3 (2)	35 (11)	17 (20)	19 (24)	
Convalescent plasma		8 (1)	2 (2)	4 (1)	NA	2 (3)	
Oxygen supplementation	617	596 (97)	116 (94)	315 (97)	86 (100)	78 (98)	0.069
High-flow nasal cannula	576	190 (33)	19 (16)	86 (28)	41 (53)	44 (56)	<0.001*
Intensive Care Unit (ICU) admission	617	252 (41)	18 (15)	90 (28)	82 (95)	62 (78)	<0.001*
Length of stay in ICU in days	249						
mean (SD)		21.7 (17.6)	11.4 (12.4)	12.7 (10.9)	32.1 (20.0)	24.2 (15.2)	<0.001*
median (IQR)		16.0 (9.0–31.0)	8.0 (3.5–11.8)	9.0 (6.0–16.3)	29.0 (17.5–40.5)	19.0 (13.0–38.3)	
Invasive mechanical ventilation	617	216 (35)	11 (9)	67 (21)	79 (92)	59 (74)	<0.001*
Duration of intubation in days	209						
mean (SD)		19.5 (14.2)	13.4 (12.2)	12.6 (8.5)	25.9 (16.0)	20.4 (13.5)	<0.001*
median (IQR)		14.0 (8.0–28.0)	8.0 (6.0–18.0)	9 (6.0–19.0)	24.0 (13.0–34.3)	14 (10.0–32.5)	
Tracheostomy	601	79 (13)	3 (2)	15 (5)	39 (47)	24 (33)	<0.001*
Delirium	615	148 (24)	16 (13)	40 (13)	51 (63)	41 (54)	<0.001*
Thrombosis	601	94 (16)	8 (7)	36 (11)	29 (35)	21 (27)	<0.001*
Time interval between hospital discharge and study follow-up in days, mean (SD)							
3-month visit	431	95.5 (14.4)	95.4 (13.4)	93.6 (25.2)	98.1 (16.9)	98.6 (20.0)	0.317
6-month visit	510	185.1 (27.6)	186.4 (13.1)	184.2 (34.4)	186.0 (17.8)	186.1 (18.5)	0.888
12-month visit	489	368.5 (18.4)	365.1 (12.0)	369.4 (20.9)	366.7 (9.7)	372.1 (21.1)	0.080

Data are presented as n (%) unless otherwise indicated. Com-rehab, group with community-based rehabilitation in care pathway; Med-rehab, group with medical rehabilitation in care pathway; NA, Not Applicable; No-rehab, group without rehabilitation in care pathway; SNF-rehab, group with skilled nursing rehabilitation in care pathway.

[a] Because of small group sizes per care pathway we analyzed migration background as 'European' versus all non-European data, and treatment as 'No treatment' versus all other treatment data combined.

[b] p-values are based on independent *t*-test, Kruskal-Wallis test, Chi-square test, or Fisher's Exact test as appropriate.

* Significant p-values with Bonferroni correction ($p \leq 0.001$).

Table 2
Estimated mean scores of 2 cognitive and 3 psychological outcome measures that were administered to participants at 3, 6, and 12 months after hospitalization for COVID-19 as part of the CO-FLOW study.

	3 months	6 months	12 months	p-value [a]	p-value [b]	p-value [c]
MoCA	22.8 (0.2)	23.6 (0.2)	24.1 (0.2)	<0.001	<0.001	0.004
CFQ	29.7 (0.8)	29.8 (0.8)	30.8 (0.8)	0.069	0.730	0.040
IES-R	14.7 (0.6)	12.7 (0.6)	12.3 (0.6)	<0.001	<0.001	0.333
HADS-A	5.4 (0.2)	4.9 (0.2)	4.9 (0.2)	<0.001	<0.001	0.997
HADS-D	5.1 (0.2)	4.6 (0.2)	4.6 (0.2)	<0.001	0.001	0.503

Data are presented as estimated mean (standard error) based on generalized estimating equations. CFQ, Cognitive Failure Questionnaire; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale; IES-R, Impact of Event Scale-Revised; MoCA, Montreal Cognitive Assessment.
[a] p-value illustrates total trajectory from 3 to 12 months.
[b] p-value illustrates trajectory from 3 to 6 months.
[c] p-value illustrates trajectory from 6 to 12 months.

rehab, 33 (25–45) days and SNF-rehab, 33 (20–41) days. Twelve participants in the Med-rehab group received outpatient rehabilitation only. Compared to other care pathways, participants in the SNF-rehab group were significantly older, 66.1 (9.6) years, and had more comorbidities (91%). Participants in the Med-rehab group had the longest hospital LOS at 44 (32–55) days, the most men (78%), and the highest incidence of ICU admission (95%), obesity (61%), and employment (86%), compared to other care pathways.

Cognitive functioning outcomes

Cognitive deficits

Among participants with cognitive deficits at their first assessment, we observed improvement over time (MD 1.30, 95% CI 0.89 to −1.72; p<0.001), significant improvement from 3 to 6 months (MD 0.79, 95% CI 0.4 to 1.19; p<0.001), and from 6 to 12 months (MD 0.51, 95% CI 0.16 to 0.86; p = 0.004) (Table 2). At 3 months, 42% (179/428) of participants had cognitive deficits; at 6 months the frequency was 30% (145/487); and at 12 months it was 21% (101/474) (Fig. 2; Supplemental Table 1). Participants with cognitive deficits at their 12-month follow-up were more often unemployed or retired compared to participants without cognitive deficits; they also more often had a non-European migration background and lower pre-COVID educational status (Supplemental Table 2). The lowest MoCA scores were in memory, executive functioning, and language cognitive domains (Supplemental Table 3). Participants with an overt language barrier (23/617) were not evaluated with the MoCA tool.

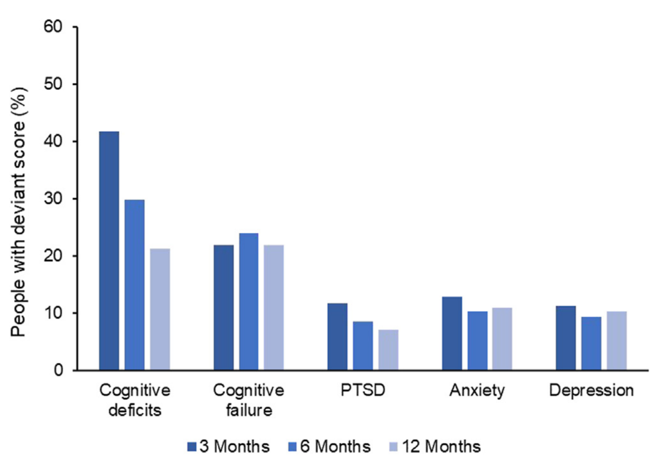

Fig. 2. Graph showing the percentage (shown on the y-axis) of 617 participants from the CO-FLOW study with one or more deviant outcome scores (shown on the x-axis) at 3, 6, and 12 months after hospitalization for COVID-19.

CFQ, Cognitive Failure Questionnaire, a score >43 indicates cognitive failure; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale, a score ≥11 indicates anxiety; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale, a score ≥11 indicates depression; IES-R, Impact of Event Scale-Revised, a score IES-R ≥33 indicates a diagnosis of posttraumatic stress disorder (PTSD); MoCA, Montreal Cognitive Assessment, a score <26 indicates cognitive deficits.

The Med-rehab group had the lowest percentage of participants with cognitive deficits, and the SNF-rehab group had the worst cognitive scores and highest percentage of participants with cognitive deficits at all follow-up times (Fig. 3A; Supplemental Tables 4 and 5). At 3 months, the cognitive scores between the care pathways did not differ significantly. At 12 months, the Med-rehab group scored significantly higher than the SNF-rehab group (MD 1.11, 95% CI 0.07 to 2.15; p = 0.036).

Among participants with cognitive deficits, we observed significant improvement from 3 to 12 months in the No-rehab (MD 2.32, 95% CI 1.47 to 3.17; p<0.001); Com-rehab (MD 1.27, 95% CI 0.77 to 1.78; p<0.001); and Med-rehab (MD 1.63, 95% CI 0.17 to 3.10; p = 0.029) groups; but not in the SNF-rehab group (MD 0.18, 95% CI −0.97 to 1.33; p = 0.094) (Fig. 3B; Supplemental Table 4). At 12 months, the SNF-rehab group had the highest prevalence of cognitive deficits (22/59, 37%); their MoCA scores were significantly worse than those of the No-rehab (MD −2.38, 95% CI −3.91 to −0.85; p = 0.002), Com-rehab (MD −1.44, 95% CI −2.83 to −0.06; p = 0.042), and Med-rehab (MD −1.98, 95% CI −3.70 to −0.27; p = 0.024) groups.

Cognitive failure

In the full cohort, no significant changes occurred in cognitive failure over time (p = 0.069) (Table 2). At 3 months, 22% (95/433) of participants experienced cognitive failure; at 6 months, 24% (114/476);) and at 12 months, 22% (101/462) (Fig. 2; Supplemental Table 1).

At 3 months, the No-rehab group had the lowest cognitive failure scores; significantly lower than the Com-rehab (MD −5.77, 95% CI −9.81 to −1.73; p = 0.005) and SNF-rehab (MD −6.76, 95% CI −12.95 to −0.56; p = 0.033) groups (Fig. 4A; Supplemental Table 4). At 3 months, 25% (61/246) of the Com-rehab group had cognitive failure, the highest incidence compared to the other groups (Supplemental Table 5). From 3 to 6 months, the cognitive failure score significantly increased only in the Med-rehab group (MD 4.24, 95% CI 1.63 to 6.84; p = 0.001). From 6 to 12 months, the cognitive failure scores did not change significantly for any care pathway. At 12 months, the Med-rehab group showed the highest cognitive failure score; significantly higher than the No-rehab (MD 11.84, 95% CI 4.95 to 18.72; p<0.001) and Com-rehab (MD 6.30, 95% CI 0.13 to 12.48; p = 0.046) groups. The No-rehab group scored also significantly lower than Com-rehab (MD −5.53, 95% CI −9.47 to −1.59; p = 0.006) and SNF-rehab (MD −6.84, 95% CI −12.49 to −1.20; p = 0.018) groups. Of all care pathways, the Med-rehab group had the highest prevalence of cognitive failures (18/64, 27%) at 12 months.

Psychological outcomes

PTSD

In the full cohort, PTSD scores decreased significantly over time (MD −2.45, 95% −3.31 to −1.59; p<0.001), with a significant decrease from 3 to 6 months (MD −2.11 95% −2.91 to −1.31; p<0.001) (Table 2). At 3, 6, and 12 months the prevalence of PTSD was 12% (51/435), 9% (41/484), and 7% (34/472), respectively (Fig. 2; Supplemental Table 1).

At 3 months, No-rehab had the lowest prevalence (3/81, 4%) of PTSD of all groups (Fig. 4B, Supplemental Tables 4 and 5). Their PTSD score was significantly lower than the Com-rehab (MD −5.85, 95% CI −8.43 to −3.28; p<0.001), Med-rehab (MD −7.12, 95% CI −12.73 to −1.51; p = 0.013), and SNF-rehab (MD −8.81,

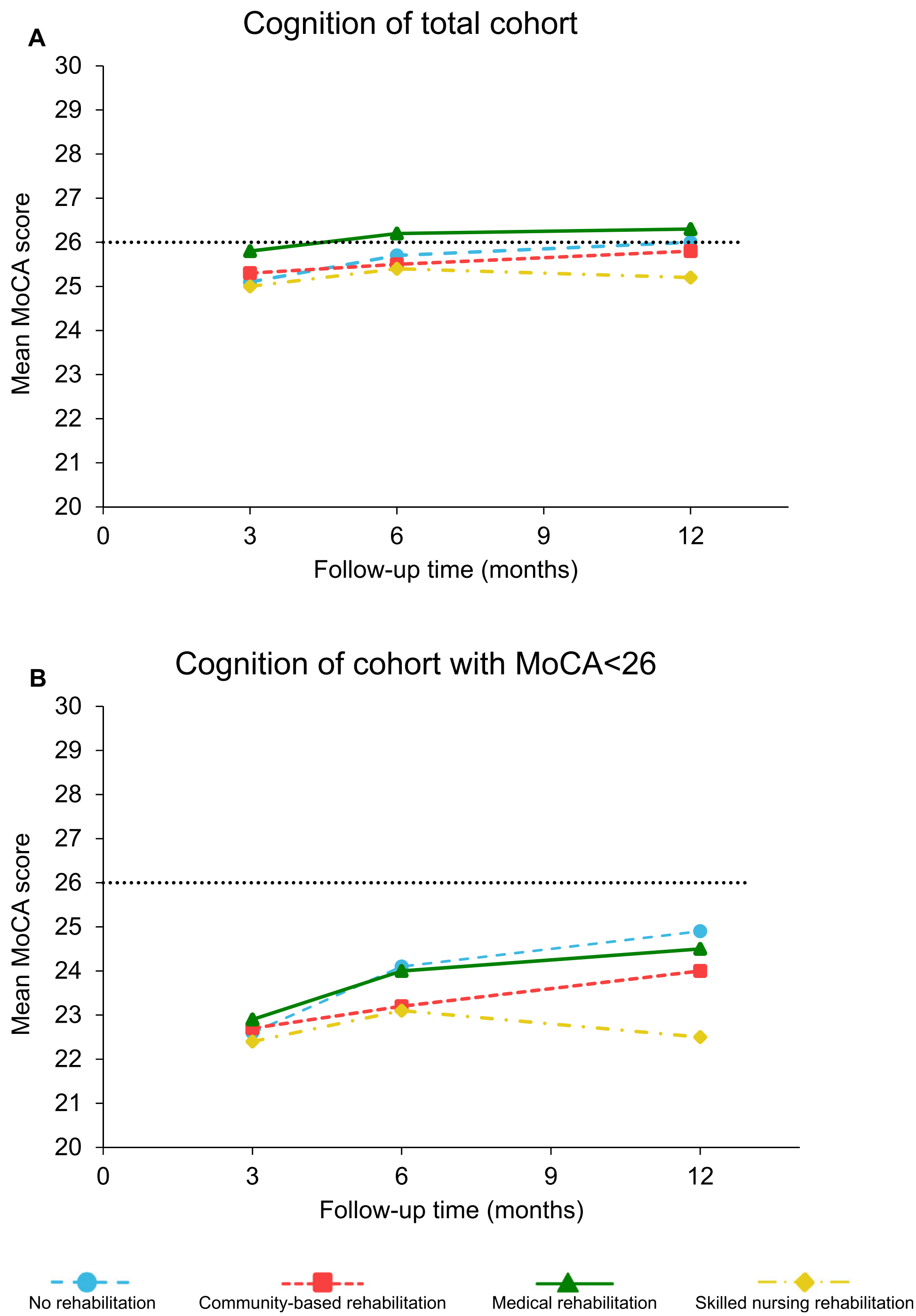

Fig. 3. Graphs showing the estimated mean Montreal Cognitive Assessment (MoCA) scores of 617 participants scores at 3, 6, and 12 months (x-axis) after hospitalization for COVID-19. Data were grouped by the 4 different care pathways as part of the CO-FLOW study. Participant MoCA score is shown along the y-axis; the dotted line at 26 refers to the MoCA score below which a cognitive deficit is indicated. In (A) the mean MoCA scores for all 617 participants in each care pathway group are shown; when participants had a MoCA score of ≥26, this score was re-used as their score for subsequent time points. The MoCA was only repeated at the next visit if the score was <26. In (B) the mean MoCA scores are presented only for those participants in each care pathway group who scored <26 at 3 and/or 6 months, to show their improvement over time. Means are adjusted for age at admission, sex, body mass index at admission, pre-COVID employment status, and length of hospital stay. None of these covariables were found to have contributed significantly to the model.

95% CI −13.58 to −4.03; $p<0.001$) groups. From 3 to 6 months, the PTSD scores for all participants reduced; this reduction was significant for the Com-rehab (MD −2.43, 95% CI −3.50 to −1.37; $p<0.001$) and SNF-rehab (MD −3.32, 95% CI −5.70 to −0.95; $p = 0.006$) groups. At 12 months, the Com-rehab (MD 3.63, 95% CI 1.08 to 6.18; $p = 0.005$), Med-rehab (MD 7.54, 95% CI 2.52 to 12.55; $p = 0.003$), and SNF-rehab (MD 6.96, 95% CI 2.79 to 11.12; $p = 0.001$) groups had a higher PTSD score than No-rehab. Participants in Med-rehab had the highest prevalence (11/73, 15%) of PTSD symptoms.

Anxiety

In the full cohort, anxiety scores decreased significantly over time (MD −0.51, 95% CI −0.80 to −0.21; $p<0.001$), although the decrease was significant only from 3 to 6 months (MD −0.51, 95% CI −0.77 to −0.25; $p<0.001$) (Table 2). The prevalence of anxiety at 3 months was

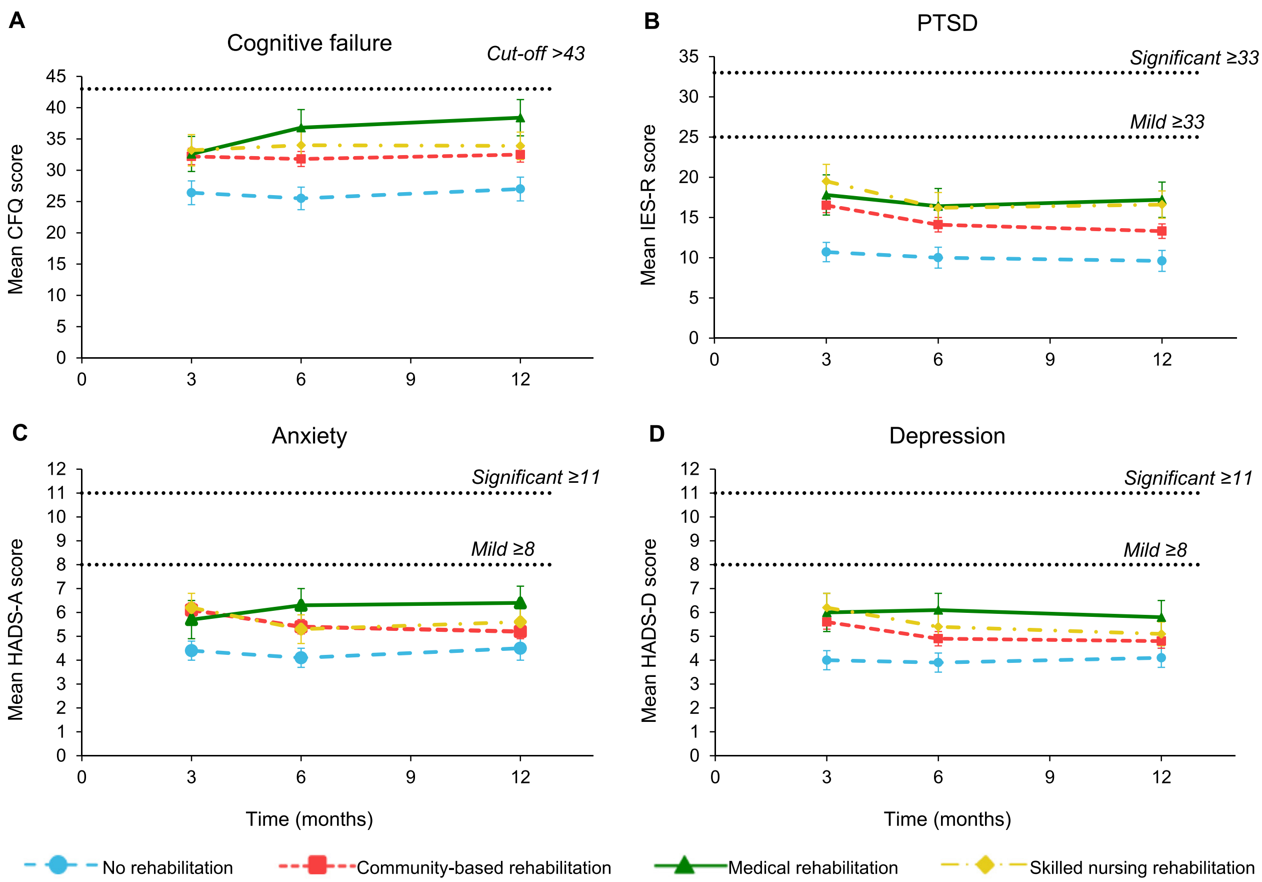

Fig. 4. Graphs showing the estimated mean scores of the (A) Cognitive Failure Questionnaire (CFQ); (B) Impact of Event Scale-Revised (IES-R) for identification of posttraumatic stress disorder (PTSD); (C) Hospital Anxiety and Depression Scale - Anxiety subscale (HADS-A); and (D) Hospital Anxiety and Depression Scale - Depression subscale (HADS-D) in 617 participants at 3, 6, and 12 months after hospitalization for COVID-19. Data were grouped by the 4 different care pathways as part of the CO-FLOW study. For each graph, scores above the dotted lines indicate either a mild (lower line) or significant (upper line impairment for) impairment for each outcome.

CFQ, Cognitive Failure Questionnaire, a score >43 indicates cognitive failure; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale, a score ≥8 indicates mild, a score ≥11 indicates significant anxiety; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale, a score ≥8 indicates mild, a score ≥11 indicates significant depression; IES-R, Impact of Event Scale-Revised, a score ≥25 indicates mild, a score ≥33 indicates significant posttraumatic stress disorder (PTSD). Means were adjusted for participant age at admission, sex, body mass index at admission, pre-COVID employment status, and length of hospital stay. The following covariables contributed significantly to the models: for cognitive failure, age at admission (p = 0.011), sex (p<0.001), and length of hospital stay (p<0.001); for anxiety, age at admission (p = 0.042), and sex (p<0.001); for depression, sex (p = 0.047); for PTSD, age at admission (p = 0.004), and sex (p<0.001).

13% (56/436); at 6 months, 10% (50/486); and at 12 months, 11% (52/474) (Fig. 2; Supplemental Table 1). Anxiolytic medication was taken by 8/380 (2%) participants at 3 months; 17/436 (4%) at 6 months; and 2/422 (1%) at 12 months; at the same time points, a psychologist saw, respectively, 49/380 (13%), 48/436 (11%), and 18/422 (4%) of participants who had scored below the cutoff. Of participants who scored above the cutoff, anxiolytic medication was taken by 3/56 (5%) participants at 3 months, and 2/50 (4%) at 6 months; 22/56 (39%) saw a psychologist at 3 months, 18/50 (36%) did so at 6 months, and 10/52 (19%) at 12 months.

At 3 months, the No-rehab group had a significantly lower anxiety score than Com-rehab (MD −1.68, 95% −2.52 to −0.84; p<0.001) and SNF-rehab (MD −1.77, 95% CI −3.16 to −0.38; p = 0.013) groups; the No-rehab group also had the lowest prevalence (3/80; 4%) of anxiety among all groups (Fig. 4C; Supplemental Tables 4 and 5). From 3 to 6 months, anxiety scores decreased significantly in the Com-rehab (MD −0.67 95% CI −1.02 to −0.32; p<0.001) and SNF-rehab (MD −0.92, 95% CI −1.58 to −0.27; p = 0.006) groups; it decreased non-significantly in the No-rehab (MD −0.37, 95% CI −0.92 to 0.19; p = 0.2), and increased non-significantly Med-rehab (MD 0.57, 95% CI −0.27 to 1.41; p = 0.182) groups. From 6 to 12 months, no significant changes occurred. At 12 months, the Med-rehab group had the highest prevalence of anxiety (12/73, 16%) while 5% (4/73) consulted a psychologist. This group had significantly higher anxiety scores than the No-rehab (MD 1.97, 95% CI 0.27 to 3.66; p = 0.023) group.

Depression

In the full cohort, depression scores decreased significantly over time (MD −0.55, 95% CI −0.84 to −0.25; p<0.001); this change was only significant from 3 to 6 months (MD −0.46, 95% CI −0.73 to −0.18; p = 0.001) (Table 2). At 3, 6, and 12 months, depression was reported in 11% (49/436), 9% (45/484), and 10% (49/475) of participants, respectively (Fig. 2; Supplemental Table 1). Among participants who scored below the cutoff, 20/387 (5%), 20/439 (5%), and 12/426 (3%) took antidepressant medication at 3, 6, and 12 months, respectively. In addition, at the same time points, 53/387 (14%), 52/439 (12%), and 20/426 (5%), respectively, consulted a psychologist. For those participants who scored above the cutoff, 3/49 (6%) took antidepressant medication at 3 months; 6/45 (13%) at 6 months, and 1/49 (2%) at 12 months. At the same time points, a psychologist was seen by 18/49 (37%), 13/45 (29%), and 9/49 (18%) participants, respectively.

At 3 months, the No-rehab group showed significantly lower depression scores than the Com-rehab (MD −1.52, 95% CI −2.36 to −0.68; p<0.001), Med-rehab (MD −1.94, 95% CI −3.76 to −0.12;

p = 0.037) and SNF-rehab (MD −2.19, 95% CI −3.58 to −0.80; p = 0.002) groups. The No-rehab group also had the lowest prevalence of depression (2/80, 3%) compared to other groups (Fig. 4D; Supplemental Tables 4 and 5). From 3 to 6 months, depression scores decreased significantly in the Com-rehab (MD −0.60, 95% CI −0.96 to −0.25; p<0.001) and SNF-rehab (MD −0.80, 95% CI −1.47 to −0.13; p = 0.019) groups, but not in the No-rehab (MD −0.17, 95% CI −0.81 to 0.47]; p = 0.605) or Med-rehab (MD 0.15, 95% CI −0.85 to 1.16; p = 0.764) groups. From 6 to 12 months, no significant changes were found. At 12 months, the Med-rehab group showed a higher depression score than No-rehab (MD 1.76, 95% CI 0.17 to 3.35; p = 0.03. The highest prevalence of depression occurred in the Med-rehab and SNF-rehab groups (both 12/73, 16%): 6% (4/73) of Med-rehab participants and 1% (1/73) of SNF-rehab participant consulted a psychologist.

Correlation between cognitive and psychological outcomes

In the full cohort, cognitive deficits and/or cognitive failure were experienced by 48% (237/494) of participants at 3 months, 43% (230/530) at 6 months, and 38% (188/498) at 12 months. At least one clinically significant psychological impairment was experienced by 21% (91/440) of participants at 3 months; this decreased to 18% (87/494) at 6 months and 15% (74/482) at 12 months. At 12 months, cognitive failure, PTSD, anxiety, and depression were moderately associated; Spearman's correlation coefficients ranged from 0.559 to 0.728. Cognitive deficits were not associated with any of the self-reported cognitive and psychological outcomes ($r \leq 0.2$) (Supplemental Table 6).

Discussion

This is the first study to have longitudinally assessed outcomes across multiple rehabilitation settings in survivors of COVID-19 up to 12 months. The No-rehab group showed good cognitive recovery and reported the fewest psychological sequelae; possibly because participants were a priori the least severely injured. The SNF-rehab group had the most cognitive deficits and some self-reported cognitive failure. This group was composed of older people and more retirees; our findings thus agreeing with previous reports of COVID-19 recovery in older people [11,37].

Objectively, Med-rehab participant data indicated that they made a good cognitive recovery, yet this group also had the most psychological sequelae at 12 months. The large improvement in cognitive deficits within 6 months therefore seems unexpected. This group was the most severely affected by COVID-19: they had the longest hospital stay, highest rates of ICU admission, and most incidents of delirium and thrombosis. However, the Med-rehab participants were also the youngest people in the study with the highest employment rates pre-COVID. Thus, our findings may also be explained not only by younger age and cognitive therapy, but also the greater cognitive function challenges these people encountered on their return to work in areas such as attention, information processing, and working memory, all of which may have improved their recovery [38,39].

The Med-rehab group experienced the most cognitive failure up to 12 months. This seems contradictory, as they showed improvements in cognitive deficit scores. However, objectively-measured and subjectively-reported cognitive difficulties are not necessarily correlated [40]. Voruz et al. suggested this could be due to anosognosia, an impaired self-perception of cognitive deficiencies. Thus, people might have high, objectively-measured cognitive deficit scores, but not perceive their cognitive failure due to anosognosia [41]. Previous studies have shown that subjectively-reported cognitive difficulties are associated with psychological problems and fatigue in people hospitalized for COVID-19 [42,43,44]; something we also observed. At 12 months, Med-rehab participants reported the most psychological symptoms associated with more cognitive failure. This group of people were initially referred for inpatient rehabilitation but could have experienced increased physical, cognitive, and psychological demands once discharged home, potentially leading to the higher rates of cognitive failure and psychological symptoms, such as depression [45,46]. Therefore, after Med-rehab discharge such people might benefit from additional (vocational) rehabilitation programs and/or psychological coaching. A longer follow-up is needed to evaluate this pattern and long-term outcomes.

The largest care pathway group (Com-rehab) received monodisciplinary rehabilitation in the community; most often an outpatient physical therapy program. Surprisingly, one fifth of this group had cognitive deficits and a relatively high prevalence of self-reported cognitive failure over 12 months. Although their psychological status improved over time, anxiety and depression levels were not much lower than in the other rehabilitation groups. As described above, these psychological symptoms could explain the high prevalence of cognitive failure [42,44]. Persistent cognitive deficits should be further investigated to identify those people who would normally only be offered physical therapy who might instead require cognitive or psychological follow-up support.

Although overall cognitive deficits decreased over time, at 12 months after hospital discharge the incidence remained at 21% (101/474). Another similar study over 12 months reported cognitive deficits in 16% of people [18]. This is lower than our reported levels for the No-rehab (17/92, 19%), Com-rehab (54/259, 21%), and SNF-rehab (22/59, 37%) participants, but not for Med-rehab participants (8/70, 11%). The difference may be because 47% of participants of the other study were discharged to rehabilitation centers, compared to 14% of our cohort. We also observed fewer cognitive deficits in the Med-rehab group. Differences in cohort demographics might also be involved, as participants with a non-European background, a lower pre-COVID educational status, or who were pre-COVID unemployed or retired had a lower MoCA score. Furthermore, changes in brain structure associated with cognitive decline have been reported after comparing brain scans from individuals before and after COVID-19 to those from a well-matched control group, which may also explain cognitive deficits [47]. Follow-up is required to investigate such long-term effects.

Studies of post-COVID psychological outcomes report PTSD in 5–6% of people, anxiety in 9–26%, and depression in 6–11%, up to 15 months later [5,18,19,26]. These psychological sequelae after ICU treatment are described as the post-intensive care syndrome [48]. We found a higher prevalence of PTSD and depression in the Med-rehab and SNF-rehab groups, care pathways that were often provided after ICU treatment. However, the prevalence of psychological impairments was low and comparable to the Dutch norm at 12 months, indicating good psychological recovery [49,50].

Our study has some limitations. First, not all participants had a 3-month follow-up visit. Second, migration background might have influenced MoCA outcomes, as participants with a language barrier were excluded from the MoCA test. Third, the high prevalence of comorbidities like cardiovascular or pulmonary disease might have influenced MoCA outcomes as they also cause cognitive deficits. Fourth, by not repeating the MoCA after a score ≥26, we may have missed future deterioration in cognitive function. Fifth, the covariable adjustment might have strongly influenced the SNF-rehab results: this was the oldest population with the longest hospital stay. In addition, older age might also affect MoCA scores. Finally, we lacked information regarding participants' levels of cognitive and psychological functioning before COVID-19; therefore, we could only evaluate function relative to our first assessment.

A major strength of this study is the multicenter design with participation of hospitals and rehabilitation centers. This enabled recruitment of people from a large region of the Netherlands. Participants had a wide range of disease severity, migration backgrounds, treatment strategies, and care provision (both general ward and ICU).

Second, the repeated measurements over time enabled analysis of recovery patterns up to 12 months and facilitates comparisons with other studies. Finally, the facilities where participants received treatment after hospitalization for COVID-19 were included. Thus, we can uniquely show cognitive and psychological recovery in people with COVID-19 across all main care pathways.

Conclusions

In conclusion, people hospitalized for COVID-19 showed cognitive and psychological recovery up to 12 months after discharge, with the largest improvement in the first 6 months. The No-rehab group had the fewest sequelae. People who received rehabilitation showed continued recovery in the first 6 months, although at 12 months, cognitive function problems persisted. Multidisciplinary rehabilitation comprising cognitive and psychological support should be considered in the management of people post-COVID since the condition seems to be multifactorial. Continued follow-up assessments will allow to monitor changes in cognitive and psychological outcomes.

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Supplemental material

Supplemental Figure 1. Referral procedure for people after hospitalization for COVID-19. The multidisciplinary team consists of a pulmonologist or intensive care physician, a physical therapist, a rehabilitation physician and/or an elderly care physician.

[1] Assessment of functional impairments (physical, cognitive, and/or psychological), medical status, premorbid functional level, comorbidities, and care needs [1]

[2] Rehabilitation as defined by the World Health Organization aims to help a child, adult, or older person to be as independent as possible in everyday activities and enables participation in education, work, recreation, and meaningful life roles, such as taking care of family [2].

Skilled nursing rehabilitation focuses primarily on frail elderly with comorbidities.

Medical rehabilitation is aimed at high-intensity treatment, mostly of a younger population.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rehab.2023.101737.

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