The cognitive effects of COVID-19 in patients receiving clinical rehabilitation

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Abstract

Background: The COVID-19 pandemic has led to countless hospitalizations, intensive care unit (ICU) admissions and even transfer to rehabilitation centers. Since the pandemic is still recent, relatively little is known about the long-term cognitive consequences in the phase of the disease right after clinical rehabilitation. The aim of the current study is to investigate the long-term cognitive effects of COVID-19 in people who received clinical rehabilitation.

Methods: We included 46 patients (Mean age= 58.6 (*SD*= 7.1), 87% male), in the period from rehabilitation center admission up to 6 months post hospital discharge. Cognitive tests measuring domains of complex attention, executive functioning, and learning and memory were administered during the first days of rehabilitation. General cognitive performance was measured using the Montreal Cognitive Assessment (MoCA) at rehabilitation center discharge and at 3 and 6 months post hospital discharge. A linear mixed model analysis was used to compare MoCA scores at the different timepoints. The influence of time spent in ICU on the MoCA scores at the given timepoints was also investigated using linear regressions.

Results: The cognitive domain complex attention was most severely impaired at rehabilitation center admission, with 16.7% showing severe cognitive impairment and 29.2% showing mild cognitive impairment, followed by executive functioning, with 13% showing severe impairment and 43.5% showing mild cognitive impairment. Furthermore, global cognitive functioning improved within subjects during the period between rehabilitation center discharge and 3 months post hospital discharge (p= 0.046), but decreased between subjects in the period between 3 months post hospital discharge and 6 months post hospital discharge (p= 0.018). ICU admission time was not correlated with MoCA scores at any of the given timepoints.

Conclusions: Complex attention was most impaired at rehabilitation center admission. Global cognitive functioning increased in the period between rehabilitation center discharge and 3 months post hospital discharge and decreased in the period between 3 and 6 months post hospital discharge. These results may help optimize the future course of treatment.

Layman's abstract

Mensen die ernstig ziek worden door COVID-19 komen terecht op de spoedeisende hulp en worden daarna soms opgenomen in een revalidatiecentrum. Er is weinig informatie over de langdurige gevolgen van COVID-19 op cognitief gebied zoals problemen met concentratie, logisch nadenken en het geheugen. Dit onderzoek focust zich op 46 mensen die na de ziekenhuisopname in het revalidatiecentrum zijn opgenomen. Met de hulp van cognitieve testen die complexe aandacht (het blijven concentreren tijdens een taak), executief functioneren (logisch nadenken tijdens een taak) en leren en geheugen (informatie kunnen onthouden tijdens een taak) in kaart brengen, hebben we gekeken naar cognitieve problemen aan het begin van opname in het revalidatiecentrum.

Verder is er gekeken naar het globaal cognitief functioneren door middel van de Montreal Cognitive Assessment (MoCA), die is afgenomen bij ontslag uit het revalidatiecentrum en op 3 en 6 maanden na ziekenhuisontslag. Ook is er gekeken of de lengte van de opname op de spoedeisende hulp gerelateerd was aan de behaalde MoCA scores.

De resultaten laten zien dat bij opname in het revalidatiecentrum complexe aandacht het meest ernstig is aangedaan, namelijk bij 4 van de 24 mensen zeer ernstig aangedaan en bij 7 van de 24 mensen licht aangedaan, gevolgd door executief functioneren, waarbij 3 van de 23 mensen ernstig zijn aangedaan en 10 van de 23 mensen licht zijn aangedaan. Deze resultaten sluiten aan bij onderzoeken die eerder zijn gedaan naar de cognitieve gevolgen van COVID-19. Daarnaast nemen scores op de MoCA toe, wat een verbetering in het cognitief functioneren betekent, in de periode tussen ontslag uit het revalidatiecentrum tot 3 maanden na ziekenhuisopname bij dezelfde mensen die op die twee tijdspunten gemeten zijn. Opvallend genoeg nemen de MoCA scores weer af in de periode tussen 3 maanden na ziekenhuisopname en 6 maanden na ziekenhuisopname bij verschillende mensen die op die twee tijdspunten gemeten zijn. Daarnaast is er geconstateerd dat de tijd doorgebracht op de spoedeisende hulp niet van invloed is op de MoCA scores. Dit onderzoek kan bijdragen aan het ontwikkelen van behandelingen die focussen op de langetermijngevolgen van COVID-19.

1. Introduction

On March 11th, 2020, the Coronavirus disease-2019 (COVID-19) virus outbreak was officially branded a pandemic by the World Health Organization (WHO). Within the first half year, the virus had already caused half a million deaths and affected millions of people all over the world, leading up to around 2 million deaths in January 2021 (Alemanno et al., 2020). The virus has been described as one to cause a severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) (Cheng et al., 2020). COVID-19 symptoms can get severe enough to lead to hospitalization, including having to be taken to the ICU, followed by immediate transfer to a rehabilitation center after hospital discharge. Unfortunately, after the initial hospital admission, the aftermath of COVID-19 lingers. Because the pandemic is still so recent, relatively little is known about the cognitive and psychological effects of COVID-19 in the subacute phase of the disease. Some studies have already examined cognitive complaints after hospitalization in people who suffered from COVID-19. These studies showed persistent complaints in memory, attention and fatigue (Garrigues et al., 2020; Miners et al., 2020).

Since the pandemic started, some research has been done about the specific cognitive deficits present in people suffering from COVID-19 who are transferred to a rehabilitation center after hospital discharge after having been suspected of more elaborate physical and/or cognitive deficits. A study by Alemanno and colleagues (2020) investigated the impact of COVID-19 in patients who were referred to a COVID-19 rehabilitation hospital unit in Milan. When using the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE), the authors found that 80% of the population showed significant cognitive deficits. In that study, the MoCA was administered at rehabilitation admission and again after 1 month follow up after hospital discharge. The results of the follow up showed that MoCA scores significantly improved over the course of 1 month (Alemanno et al., 2020). The MoCA was also used as measure of global cognitive function in a study by Hosp and colleagues (2021) in patients who were hospitalized due to COVID-19. Of the 29 patients examined, 54% showed mild cognitive impairment in the subacute phase of COVID-19, while 15% showed severe cognitive impairment. The cognitive domains of memory, attention, executive function and visuoconstruction were most impaired (Hosp et al., 2021).

Focusing on deficits in specific cognitive domains, a study by Jaywant and colleagues (2020) has been conducted on hospitalized patients who required acute rehabilitation prior to hospital discharge to recover from COVID-19. The Brief Memory and Executive Test was used, divided into 8 subtests to mainly assess memory, attention and executive functioning. The results of this study showed that deficits in attention and executive functioning were most apparent, and present in 81% of the patients (Jaywant et al., 2020). A study by Almeria and colleagues (2020) examined the cognitive profile of 35 adults who were hospitalized due to COVID-19. Impaired performance was observed in 25% of the patients in tests that measured attention, memory and executive functioning (Almeria et al., 2020).

When looking at the longer-term effects of COVID-19, Garrigues and colleagues (2020) described some of the most persistent complaints in patients about 100 days after hospitalization. These consisted of fatigue, dyspnoea, memory loss, concentration problems and sleep disorders (Garrigues, 2020). However, this study did not show why these complaints persisted over time. An article by Miners and colleagues (2020) described regions of white matter damage in recovered COVID-19 patients in a 3-month post hospitalization follow-up study. This study showed disruption and lesions in the white matter in brain regions as the hippocampus, which is associated with loss of memory (Miners et al., 2020).

Another way to estimate the prevalence of (longer-term) cognitive effects of COVID is by looking at a syndrome that resembles the coronavirus SARS-Cov-2 in its symptoms, Acute Respiratory Distress Syndrome (ARDS). An article by Hopkins and colleagues (2006) describes that patients who suffered from classical ARDS had cognitive deficits at the time of hospital discharge. These deficits mainly consisted of memory impairment, attention deficits, concentration problems and impaired processing speed. A follow up study showed that patients still had significant memory problems after one year (Hopkins et al., 2006). Reported prevalence of ARDS in COVID-19 patients range from 15.6 up to 31%, with ARDS being most prevalent in hospitalized patients. Factors of ARDS that may contribute to cognitive decline are mainly sepsis and hypoxemia, which are known to result in long-term impairment of cognitive function (Hewitt et al., 2021). A global literature survey on the prevalence of ARDS in hospitalized patients due to COVID-19 reviewed over 1000 publications and 2486 cases (Tzotzos et al., 2020). The study describes a prevalence of ARDS in 33% of these patients, and transfer to ICU was prevalent in 25% of the cases. Regarding patients transferred to the ICU, 75% suffered from ARDS (Tzotzos et al., 2020). A meta-analysis by Kohler and colleagues (2019) described a positive correlation between cognitive deficits at time of discharge from the ICU and hypoxemia (oxygen saturation below 90%) in patients who suffered from ARDS (Kohler et al., 2019).

Another factor that may influence cognition of people who suffered from COVID-19 in rehabilitation is the length of stay in the ICU. ICU admission can lead to the Post Intensive Care Syndrome (PICS), which is a frequently occurring syndrome of physical, cognitive and mental disorders that develops during or after ICU stay or subsequent hospital discharge often due to psychological distress. Cognitive impairments mostly consist of deficits in memory, executive function, language, attention, and visual–spatial abilities (Inoue et al., 2019). The prevalence of PICS is higher than 70% at ICU discharge, 13-79% at 3-6 months post ICU discharge and 10-79% after one year post ICU discharge (Muradov et al., 2020). PICS may develop at a higher rate in COVID-19 patients due to the constraints in social support, longer mechanical ventilation, fear of the risk of transmission to caregivers and more sedative drug use during admission (Biehl & Sese, 2020), making it a plausible factor contributing to cognitive deficits after ICU admission due to COVID-19. A meta-analysis by Karki and colleagues (2020) showed out of 2456 ICU survivors, new cognitive impairment was present in 43% at 3 months post ICU discharge and in 25% at 6 months post ICU discharge (Karki et al., 2020). A study by Negrini and colleagues (2021) reported that impairment in memory, attention and language abilities was positively related to length of ICU stay in hospitalized patients who suffered from COVID-19 induced

ARDS (Negrini et al., 2021). As ARDS and PICS are both highly prevalent in patients who are admitted to the ICU and are associated with more severe cognitive deficits, the length of ICU admission may also be associated with more severe cognitive deficits in patients who had been admitted to the ICU with COVID-19.

When looking at the cognitive effects of COVID-19 in a rehabilitating population, it is important to know more about the specific cognitive domains that are affected and if and how cognitive functioning changes over time. The results of such research could contribute to knowledge about the extent to which cognitive functioning is affected by COVID-19, which cognitive domains are mostly affected, and what factors may contribute to this. These findings could influence the way future rehabilitation treatment is tailored to patients affected by COVID-19.

The following research questions were investigated: (1) What is the prevalence of impairment in the cognitive domains of complex attention, executive functioning, and learning and memory in COVID-19 patients at rehabilitation admission? (2) What is the prevalence of impairment in general cognitive performance at rehabilitation center discharge and does general cognitive performance improve up to 6 months follow-up after hospital discharge? (3) Is the length of ICU admission related to general cognitive performance at rehabilitation discharge and general cognitive performance over the course of 6 months?

Based on existing literature described above it is hypothesized that (1) Cognitive impairment will be present in the cognitive domains of complex attention, executive functioning and learning and memory, (2) General cognitive performance will have improved at up to 6 months post hospital discharge compared to general cognitive performance at rehabilitation center discharge, and (3.1) People with a longer ICU admission will show greater general cognitive impairment at rehabilitation discharge, and (3.2) A longer ICU admission will be associated with a lower general cognitive performance over the course of 6 months.

2. Methods

2.1 Design

The current study is a sub-study within a prospective multicenter cohort study, called 'CO-FLOW: COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system: a combined rehabilitation, pulmonary, and intensive care perspective'. The aim of the CO-FLOW study is to examine the long-term outcomes of patients with COVID-19 who survived hospitalization in the Rotterdam Rijnmond area. The study focuses on physical, cognitive and psychological functioning, measured at 3, 6, 12 and 24 months after hospital discharge. Patients who required inpatient rehabilitation are additionally tested at rehabilitation center discharge. This study focuses on the measurements at 3 and 6 months post hospital discharge and additional measurements during rehabilitation center admission and rehabilitation center discharge.

We opted to study cognitive functioning in a group of patients after hospitalization for COVID-19, who rehabilitated in Rijndam rehabilitation center. These patients were clinically suspected to have specific physical and/or cognitive impairments for which multidisciplinary care is indicated. This patient group received cognitive testing that focused on different cognitive domains during their first days at Rijndam rehabilitation center, if indicated by the rehabilitation physician. In all patients, general cognitive performance was measured at rehabilitation discharge. General cognitive performance was measured again at 3 or 6 months post hospital discharge, depending on whether patients were discharged from the rehabilitation at that time. The current study is a cohort study with both a cross-sectional and longitudinal design.

This study was conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). CEP number: NL74252.078.20. Permission from the Medisch Ethische Toetsingscommissie (METC) was granted on 23/06/2020 with number MEC-2020-0487. Patients signed an informed consent during rehabilitation center admission before the start of the study measurements.

2.2 Participants

Participants were recruited by a research assistant of the CO-FLOW study within the first days of entering rehabilitation center Rijndam. The participants that were included into the CO-FLOW study were (1) patients diagnosed with COVID-19, tested positive using a Polymerase Chain Reaction (PCR) test (Yüce et al., 2021), and (2) who were discharged from one of the seven hospitals in the Rotterdam-Rijnmond region (Erasmus MC, Ikazia, Maasstad, IJsselland, Franciscus Gasthuis, Albert Schweitzer, Reinier de Graaf Gasthuis), or treated in Rijndam rehabilitation center, Aafje or Laurens nursing home in Rotterdam after initial hospitalization, (3) who were at least 18 years old, (4) who had a good command of the Dutch language, both in written and oral form.

For the current study, only patients who were transferred to Rijndam rehabilitation center were included. The sample size of the CO-FLOW study has been estimated at over 650 patients. For this sub-study, 46 patients (Mean age= 58.6 (*SD*= 7.1), 87% male) who rehabilitated at Rijndam rehabilitation center were recruited. Indication for rehabilitation center admission was based on guidelines for Indicatiestelling Medisch Specialistische Revalidatie (2016). Participants were recruited between July 2020 and January 2021.

2.3 Measures

Demographic and clinical characteristics

Demographic characteristics were extracted from questionnaires used in the CO-FLOW study and clinical information from electronic patient records. Data consisted of age, gender, years of education, pre-COVID-19 chronic disease prevalence, number of days hospitalized, and length of stay (days) in the ICU.

Cognitive functioning

Global cognitive functioning was measured using the Montreal Cognitive Assessment (MoCA) (Nasreddine, 2005). This test was designed to serve as a relatively short cognitive screening tool to detect mild cognitive impairment and dementia (Nasreddine, 2005). The MoCA is used in leading research on cognitive functioning after COVID-19 (Alemanno et al., 2020; Patel et al., 2021). The test can be administered in approximately 10 minutes and is divided into the following items: A short-term memory recall task, a clock drawing task, a three-dimensional cube copying task, an alternation task (a short version of the Trail Making B task), a phonemic fluency task, a verbal abstraction task, a target detection sustained attention task, a serial subtraction task, a digit forward and backward task, an animal naming task, repetition of two complex sentences, and asking for the date and place of the assessment. Scores range from 0 to 30, where a score lower than or equal to 25 is indicative of global cognitive impairment. The MoCA score was adjusted for educational level, adding 1 point to the total score of individuals with ≤ 12 years of education (Nasreddine et al., 2005). The MoCA's sensitivity to detect mild cognitive impairment (MCI) is 90%, which is considered excellent (Nasreddine, 2005). Internal consistency was good (Cronbach alpha = 0,83). The discriminant validity of the MoCA as a measure for MCI was described as good (0,74) (Hoops et al., 2009).

The Trail Making Test (TMT) was used to measure divided visual attention and processing speed (Reitan et al., 1985). This test consists of part A and B. TMT-A requires patients to draw a line connecting circles numbered 1 to 25 randomly distributed on a piece of paper in ascending order. TMT-B requires patients to connect circles alternating between numbers (1 to 13) and letters (i.e., 1-A, 2-B etc.). Both tasks needed to be performed as precise and fast as possible (Periáñez et al., 2004). TMT-A and TMT-B mainly measure sustained attention (van der Elst et al., 2006). The scores on both TMT-A and TMT-B were based on the time a person takes to complete each trial in seconds. A higher score on both TMT-A and TMT-B indicates a more deviating performance. T scores were calculated based on norm scores corrected for gender, age and educational level (Schmand, 2012). According to the Cotan rating the TMT has insufficient reliability, insufficient construct validity and insufficient criterion validity (Egberink et al, 2009-2021). However, the TMT is seen to have high ecological validity and has proven to be able to distinguish healthy elderly from neurological patients as well as to predict clinical and function changes in patients with mild cognitive impairment (Llinàs-Reglà, 2017).

The Stroop task consists of three different conditions. In condition 1, the patient was asked to read names of colors printed in black ink. In condition 2, the patient had to name different color patches. In condition 3, color words were printed in an inconsistent ink color (i.e., the word blue is printed in red ink). The patient was required to name the color of the ink instead of reading the color. The Stroop task was used to measure attention, processing speed, cognitive flexibility, working memory and inhibition (Scarpina & Tagini, 2017). The T scores on all 3 conditions of the Stroop task were based on the time a person takes to complete each trial in seconds. T scores were calculated based on norm scores, corrected for gender, age and educational level (Schmand, 2012). According to the Cotan rating the Stroop task has good reliability, sufficient construct validity and insufficient criterion validity (Egberink et al, 2009-2021).

The Location Learning Test (LLT) was used to measure visuo-spatial memory (Kessels et al., 2012). The test consisted of a 5 x 5 stimulus card with 10 everyday objects located randomly on the card. After the learning phase, an empty grid card was laid out, and the objects were presented on little cards. The patient had to put them back at their original position. This exercise was repeated five times, or until the patient had completed two correct trials in a row (Kessels at al., 2006). Scores were presented in the form of the total location error and a postponed recognition score. Higher scores indicated a more impaired performance. Test scores were determined and corrected using the norms of the Maastricht Aging Study. T scores were corrected for gender, age and educational level (van der Elst et al., 2006). According to the Cotan rating the LLT had insufficient reliability, insufficient construct validity and insufficient criterion validity (Egberink et al, 2009-2021). However, the LLT is proven to correlate well with comparable tests to the MoCA such as the Mini Mental State Exam (Bucks & Willison, 2007).

The Wechsler Adult Intelligence Scale (WAIS)-III Digit Span was used to measure attention span and working memory (Wechsler, 1997). Patients were required to repeat a sequence of digits in either the same order or in reversed order. The maximum scores on the forward and backward span are 16 and 14. The higher the score, the better the performance. The score was based on the length of the sequence a person could repeat without failure. T scores were corrected for gender, age and educational level (Schmand, 2012). According to the Cotan rating the WAIS-III Digit Span had a good reliability, sufficient construct validity and insufficient criterion validity (Egberink et al, 2009-2021).

The verbal category fluency task and the verbal word fluency task were used to measure semantic memory and executive functioning. During the category fluency task the patient had to name as many words as possible that fit in a particular category in a given amount of time. The categories used in this research were animals, professions and supermarket items. During the word fluency task, the patient had to name as many words as possible starting with a particular letter in a given amount of time (60 seconds). The scores on each test were the number of correct items named (Lezak et al., 2012). The higher the score, the better the performance. T scores were corrected for gender, age and educational level (Schmand, 2012). According to the Cotan rating based on the World Fluency Test (animals and professions) by Mulder and colleagues (2006) the verbal word fluency test had sufficient reliability, sufficient construct validity and insufficient criterion validity (Egberink et al, 2009-2021).

The Letter Digit Substitution Test (LDST) was used to assess processing speed. During this test, the patient had to substitute the maximum amount of randomly distributed digits with corresponding letters according to a given key in 90 seconds (Natu et al., 1995). The score was based on the amount of correctly connected digits to letters in these 90 seconds. The higher the score, the better the performance. T scores were corrected for gender, age and educational level. A study by Van der Elst and colleagues (2008) indicated a high reliability for the LDST ($r > .85$).

Table 1 shows an overview of tests that were used and the cognitive domain(s) they measured. The chosen cognitive domains were based on 3 of the 6 key domains of cognitive functioning of the DSM 5 (American Psychological Association, 2013).

Table 1

Tests and cognitive domains measured

Name Test	Main cognitive domain(s) measured
Trail Making Test-A	Complex attention
Trail Making Test-B	Executive functioning
Stroop-1	Complex attention
Stroop-2	Complex attention
Stroop-3	Executive functioning
Location Learning Test	Learning and memory
WAIS-III Digit Span	Learning and memory
Verbal Category Fluency	Executive functioning
Verbal Word Fluency	Executive functioning
Letter Digit Substitution Test	Complex attention

A total score for each cognitive domain was determined by the mean of T scores of the tests that measure a specific cognitive domain.

2.4 Procedure

All consecutive patients were approached within the first days of arrival at Rijndam rehabilitation center. A research assistant from the CO-FLOW study explained the study procedures and provided the new patients with the patient information form about the CO-FLOW study and obtained their informed consent after a reflection period of at least 24 hours.

As part of the rehabilitation program, patients underwent cognitive screening during their first days at Rijndam rehabilitation center, by a psychological testing assistant, if indicated by the rehabilitation physician. Global cognitive functioning was measured at rehabilitation center discharge and again at 3 or 6 months post hospital discharge as part of the CO-FLOW study performed by a research assistant.

At 3 and/or 6 months post hospital discharge, dependent on the time of rehabilitation center discharge, participants were invited for a study visit in addition to their regular follow-up in the hospital of their initial admission. During an appointment of 45 minutes to 1 hour, patients went through the CO-FLOW test battery, including questionnaires about demographic and clinical characteristics, and physical mobility tests. The MoCA was repeated during the visits at 3 and 6 months post hospital discharge. All patients involved in the study were granted the right to quit the study at any time.

2.5 Statistical analyses

All analyses were performed using IBM SPSS 26. The level of alpha error was set to be 0.05 in all analyses performed. Descriptive statistics, expressed as means and standard deviations (*SD*) or 95% confidence intervals for continuous variables and numbers and proportions for categorical variables, were used to explore the demographic and clinical characteristics of the sample.

To test the hypothesis that cognitive impairment will be present in the cognitive domains of complex attention, executive functioning and learning and memory, the percentage of patients scoring below a cut off T score was noted for each cognitive domain. The mean T scores of the cognitive domains learning and memory, complex attention and executive functioning were determined per patient and for the total group of patients. The prevalence of people who score below a T score cut-off point of $T < 40$, which indicated a mild deficit, and <30 for severe deficit was determined.

To test the hypothesis that general cognitive performance will have improved up to 6 months post hospital discharge compared to general cognitive performance at rehabilitation center discharge, a linear mixed model analysis was performed. In this model, MoCA score was used as the dependent variable and measurement timepoint as the independent variable. Linear mixed models can accommodate unbalanced study designs where individuals do not need to be measured at the same exact timepoints, which makes this analysis fitting for the existing data (West, 2009). Age and gender were both added as possible predictors.

To look at the development of MoCA scores over time within subjects between rehabilitation center discharge and 3 months post hospital discharge, a non-parametric variant of the independent samples *t* test, the Wilcoxon signed rank test, was used. MoCA scores obtained by same people were collected only at the timepoints of rehabilitation center discharge and 3 months post hospital discharge. When checking the assumptions to perform a independent samples *t* test, a boxplot showed lack of normal distribution of the data, which is why the choice to use the non-parametric Wilcoxon signed rank test was made.

Data about ICU admission length was collected from 31 participants. To test the hypotheses that people with a longer ICU admission will show greater general cognitive impairment at rehabilitation discharge, and a longer ICU admission will be associated with a lower general cognitive performance over the course of 6 months, two linear regressions were performed. The choice to use a regression analysis was made to take the chronological direction of the relationship into account and to be able to make a statement about the predictive value of variables. The first regression was performed to predict global cognitive function at rehabilitation center discharge based on length of ICU stay. The second regression was performed to predict the highest MoCA score obtained over 6 months based on the length of ICU stay. In both analyses, age and gender were included as possible predictors. In the second analysis, years of education was added as a possible predictor. Maximal MoCA score was determined by taking the highest score of the measurements at rehabilitation center discharge and/or at 3 months post hospital discharge and/or at 6 months post hospital discharge.

3. Results

3.1 Participants

In the CO-FLOW study, 50 patients who rehabilitated at Rijndam were included. However, for this study 46 participants were selected due to missing values as a result of incomplete data registration at the time of analysis, resulting in no available data on MoCA scores and test scores of the cognitive screening.

Demographic and clinical characteristics are described in table 2. A comorbid condition or disease was present in 93.5% of participants with heart and vascular disease being the most prominent comorbidity, present in 30.4% of participants. Lung disease such as COPD, Asthma or Cystic fibrosis was present in 6.5% of participants.

Table 2

Demographic and clinical characteristics

Demographics	N	N, % or mean (*SD*)	Minimum	Maximum
Age in years, mean (*SD*)	46	58.6 (7.1)	40	77
Gender, male N (%)	46	40 (87.0)		
Years of education, mean (*SD*)	38	15.3 (4.5)	6	26
Clinical characteristics	N	% or mean (*SD*)		
Admitted in ICU (%)	31	100		
Days spent in the ICU, mean (*SD*)	31	36.8 (21.4)	10	113
Comorbidity, N (%)	46	43 (93.5)		
Days spent in hospital, mean (*SD*)	43	50.9 (24.7)	13	163

3.2 Prevalence of impairment in specific cognitive domains

The total sample consisted of 25 participants who received specific cognitive testing at Rijndam rehabilitation center. Results showed that all of the mean T scores are between 35 to 45, indicating mild cognitive impairment to normal cognitive functioning on all cognitive tests (table 3).

Table 3

Test scores on individual cognitive tests

Individual test	N	Mean T score	Standard deviation	Minimum T score	Maximum T score
Trail Making Test-A	21	43.6	11.9	21	66
Trail Making Test-B	18	37.7	9.0	19	55
Stroop-1	20	35.8	11.6	11	58
Stroop-2	20	35.7	9.0	22	57
Stroop-3	21	40.0	9.2	28	57
Location Learning Test	21	41.7	6.7	20	52
WAIS-III Digit Span	19	44.7	12.2	25	70
Verbal Category Fluency	18	41.2	11.2	17	73
Verbal Word Fluency	18	37.2	9.4	20	56
Letter Digit Substitution Test	24	40.8	8.3	25	55

The cognitive domain complex attention was most severely impaired, with 16.7% of the participants showing severe cognitive impairment and 29.2% showing mild cognitive impairment (table 4).

Table 4

Prevalence of cognitive impairment

	Complex Attention	Executive functioning	Learning and Memory
Mean T score (*SD*)	40.2 (8.9)	39.5 (9.0)	44.0 (8.3)
T< 30, N (%)	4 (16.7)	3 (13.0)	0 (0.0)
T30-40, N (%)	7 (29.2)	10 (43.5)	7 (31.8)
T> 40, N (%)	13 (54.2)	10 (43.5)	15 (68.2)

Note: Complex attention consists of the TMT-A, Stroop-1, Stroop-2 and the Letter Digit Substitution Test. Executive functioning consists of the TMT-B, Stroop-3, Verbal Category Fluency and Verbal Word Fluency. Learning and Memory consists of the Location Learning Test and WAIS-III Digit Span. T<30 indicates severe cognitive impairment, T30-40 indicates mild cognitive impairment, T>40 indicates normal cognitive functioning.

3.3 Longitudinal changes in MoCA scores between subjects

The MoCA was administered at least at one timepoint (rehabilitation discharge, 3 months and/or 6 months post hospital discharge) in 39 participants. Of these 39 participants, 27 received the MoCA at rehabilitation discharge, 17 participants received the MoCA at 3 months post hospital discharge and 10 participants received the MoCA at 6 months post hospital discharge. Fifteen participants received the MoCA twice at any two of the given timepoints.

At rehabilitation center discharge, 9 participants (33.3%) scored beneath the <26 cut off score for cognitive impairment. At 3 months post hospital discharge, 2 people (11.8%) scored <26, and at 6 months post hospital discharge, 5 people (50%) remained to score below the cut off point. Over the course of 6 months, 11 participants' (28.2%) maximum MoCA score stayed beneath the <26 cut off score for cognitive impairment.

In order to perform a linear mixed model analysis, a QQ-plot and boxplot were used to check the linearity, normality and homogeneity of the data. The absence of autocorrelation was checked using the Durbin-Watson statistic, which had to be around 2. An unstructured covariance matrix was used in which the number of parameters for the repeated effect of the MoCA was 2, taking the correlation between the different timepoints used into account. MoCA score was added as the dependent variable. Age, gender and time of measurement were added as fixed factors. The model was used to look at significant differences on MoCA scores over time using a within subjects design.

The overall analysis revealed that the MoCA score significantly changed over the 3 timepoints (p= 0.010). Estimated mean MoCA score did not change significantly between rehabilitation discharge and 3 month follow-up (p= 0.170). A significant difference in MoCA score was seen between the measurement at rehabilitation center discharge and 6 months post hospital discharge (p= 0.018). Mean MoCA score significantly decreased between 3 months and 6 months post hospital discharge.

Looking at the post-hoc pairwise comparisons of the different timepoints, a significant difference was observed between MoCA score at 3 months post hospital discharge and MoCA score at 6 months post hospital discharge (p= 0.002). Table 5 summarizes these results.

When looking at the effects of gender and age added to the mixed model analysis, gender did not appear to have a significant effect on MoCA score (p= 0.353), neither did age (p= 0.341).

3.4 Longitudinal changes in MoCA scores within subjects

Of the 9 participants who scored <26 at rehabilitation center discharge, 4 participants received the MoCA again at 3 months post hospital discharge. A boxplot was used to check the normality of the scores, which showed a lack of normal distribution. Wilcoxon's signed ranked test revealed a two-tailed significant difference between MoCA score at rehabilitation center discharge and MoCA score at 3 months post hospital discharge (T= 10.0, p= 0.046). All scores had improved at 3 months post hospital discharge.

Table 5

Mixed Model analysis outcomes

Estimates						
Measurement time	N	Mean MoCA score (*SE*)	Score <26 N(%)	Lower bound	Upper bound	P value opposed to previous measurement
0.00	27	26.52 (0.67)	9 (33.3)	25.19	27.86	
3.00	17	27.07 (0.68)	2 (11.8)	25.70	28.45	0.170
6.00	10	24.72 (0.78)	5 (50)	23.15	26.29	0.002*

Note: Measurement time 0.00 is at rehabilitation discharge, 3.00 is at 3 months post hospital discharge and 6.00 is 6 months post hospital discharge. $P<=.05$*= significant.

3.4 Effect of length of ICU admission on MoCA score

MoCA score at rehabilitation discharge.

Before the regression analysis was conducted, mandatory assumptions for a linear regression were checked. A scatterplot and boxplot were used to explore the presence of outliers, homoscedasticity and linearity. The boxplot showed the normality of the data was not optimal. A Normal P-P Plot was used to evaluate the skewness of the distribution, indicating a good enough fit to conduct the analysis (appendix A). Independence of observations was checked using the Durbin-Watson statistic, indicating independent observations.

The first regression analysis examined the relation between ICU admission length and the MoCA scores obtained at rehabilitation center discharge. Results suggest that the MoCA score at rehabilitation discharge cannot be predicted by length of ICU admission, $F(3, 17)= 1.316$, $p= 0.630$, $R^2 = 0.100$. Age and gender were added to the regression model, showing neither age, $F(3, 17)= 1.316$, $p= 0.607$, $R^2 = 0.100$, nor gender, $F(3, 17)= 1.316$, $p= 0.587$, $R^2 = 0.100$, are significant predictors for MoCA score at rehabilitation center discharge. Results of the univariable regression analyses are summarized in table 6.

Table 6

Univariable predictors of MoCA score at rehabilitation center discharge

MoCA reva	*B*	95% CI	For *B*	*SE B*	β	*t*	*p*	R^2	Adj. R^2
		LL	*UL*						
Model								.100	-.059
Constant	28.816	20.149	37.484	4.108		7.015	0.000*		
Age	-0.040	-0.201	0.121	0.076	-.148	-0.524	0.607		
Gender	-1.447	-4.068	6.963	2.614	.132	0.554	0.587		
Length of ICU stay	-0.013	-0.072	0.045	0.028	-.140	-0.490	0.630		

Note: MoCA reva= MoCA score at rehabilitation center discharge. *B*= unstandardized regression coefficient; CI= confidence interval; *LL*= lower limit; *UL*= upper limit; *SE B*= standardized error of the coefficient; β= standardized coefficient; R^2 = coefficient of determination; Adj. R^2 = adjusted R^2 ; *P<=.05**= significant.

Maximum MoCA score

The second regression model examined the relation between ICU admission length and maximum MoCA score per person obtained in the period between rehabilitation center discharge and 6 months post hospital discharge. Results show that in this case the maximum MoCA score cannot be predicted by length of ICU admission, $F(4, 20)= 0.083$, $p= 0.990$, $R^2 = 0.105$, nor years of education $F(4, 20)= 0.083$, $p= 0.959$, $R^2 = 0.105$. When adding age and gender to the analysis, neither age $F(4, 20)= 0.083$, $p= 0.623$, $R^2 = 0.105$, nor gender, $F(2, 36)= 0.818$, $p=$ 0947, $R^2 = 0.043$, seem to be significant predictors of the maximum MoCA scores. Results of the univariable regression analyses are summarized in table 7.

Table 7

Univariable predictors of maximum MoCA score

Max MoCA	*B*	95% CI	For B	*SE B*	β	*t*	*p*	R^2	Adj. R^2
		LL	*UL*						
Model								.105	.030
Constant	28.649	20.002	37.297	4.145		6.911	0.000*		
Age	-0.034	-0.178	0.109	0.069	-.134	-0.499	0.623		
Gender	-1.00	-3.205	3.006	1.489	-.015	-0.067	0.947		
Years of education	-0.006	-0.228	0.217	0.107	-.012	-0.052	0.959		
Length of ICU stay	0.000	-0.052	0.053	0.025	.003	0.013	0.990		

Note: Max MoCA= maximum MoCA score obtained in the period between rehabilitation center discharge and 6 months post hospital discharge. *B*= unstandardized regression coefficient; CI=

confidence interval; *LL*= lower limit; *UL*= upper limit; *SE B*= standardized error of the coefficient; β= standardized coefficient; R^2 = coefficient of determination; Adj. R^2 = adjusted R^2 ; $P<=.05$*= significant

4. Discussion

The current study aimed to investigate the long-term cognitive effects of COVID-19 in a population receiving clinical rehabilitation. The goal was to create a better understanding of the prevalence of cognitive deficits and development of cognitive functioning over time and to possibly link these cognitive deficits to ICU admission time.

We explored the prevalence of impairment in specific cognitive domains at rehabilitation center admission. When looking at the scores on the tests measuring the three cognitive domains of complex attention, executive functioning and learning and memory, mean T scores indicated mild cognitive impairment to normal cognitive functioning on all three cognitive domains at rehabilitation center admission. The cognitive domain complex attention was most severely impaired, with 16.7% showing severe impairment and 29.2% showing mild impairment, followed by executive functioning, with 13% showing severe impairment and 43.5% showing mild impairment. In the domain of learning and memory, no severe cognitive impairment was observed and 31.8% showed mild cognitive impairment. These findings are in line with existing literature on cognitive deficits in patients who suffered from COVID-19, suggesting attention and executive functioning were mostly impaired in patients receiving rehabilitation after initial hospital admission (Jaywant et al. 2020; Patel et al., 2021). The prevalence of impairment is similar as found in other studies in adults who were hospitalized due to COVID-19 (Almeria et al., 2020).

The prevalence of cognitive impairment in COVID-19 seems to be in accordance with studies describing cognitive deficits in patients who suffered from ARDS after initial hospital admission (Hopkins et al., 2006; Mikkelsen et al., 2009). In severe COVID-19, ARDS is almost always diagnosed, leading to hospitalization and possibly exposure to mechanical ventilation (Beaud, 2021). Whether ARDS has been clinically diagnosed in our patient group remains unclear, but it seems to be a plausible explanation for the similarity in cognitive deficits seen in both diseases.

Furthermore, it was hypothesized that general cognitive performance will have improved at up to 6 months post hospital discharge compared to general cognitive performance at rehabilitation center discharge. We demonstrated that MoCA scores increased within patients in the period from rehabilitation center discharge to 3 months post hospital discharge, representing an improvement in general cognitive performance. However, MoCA scores decreased again between patients in the period between 3 months post hospital discharge and 6 months post hospital discharge, suggesting cognitive decline. The increase in MoCA is in accordance with results found in another study using the MoCA, which indicated increases in MoCA scores as soon as after 1 month post rehabilitation center admission (Alemanno et al. 2020). The decrease in MoCA score between 3 and 6 months post hospital discharge opposes other research. Based on the data used in this study, results suggest that the course of cognitive function after COVID-19 over time may not be as predictable as we think. More research should be devoted to investigating why the course of cognitive functioning could fluctuate over time and what factors unique to COVID-19 may contribute to this fluctuation.

Important to note is that an additional comparison of MoCA scores between rehabilitation center discharge and 3 months post hospital discharge could be made using test scores of the same person on both timepoints. However, for the comparison of MoCA scores between 3 and 6 months post hospital discharge MoCA scores on both timepoints of different people were used. Unfortunately, for the 10 people who received the MoCA at 6 months post hospital discharge, no previous MoCA measurement was available. This made within subjects comparison at this timepoint impossible, leaving these results hard to generalize and interpret. However, when looking at within subjects comparison of MoCA score in people who scored their first MoCA at rehabilitation discharge <26 and again after 3 months post hospital discharge, MoCA scores all improved significantly. These findings are in accordance with the study done by Alemanno and colleagues (2020), investigating MoCA scores over time within subjects (Alemanno et al., 2020). The fact that only 4 participants were available in this analysis has to be kept in mind.

Furthermore, it was expected that people that with a longer ICU admission would show greater general cognitive impairment at rehabilitation discharge, and that a longer ICU admission would be associated with a lower maximum MoCA score over the course of 6 months. Our results suggest that the MoCA score at rehabilitation discharge and the maximum MoCA score over 6 months follow-up cannot be predicted by length of ICU admission. These results oppose existing literature stating ICU admission length may relate to the level of severity of PICS and cause cognitive impairment (Inoue et al., 2019; Muradov et al., 2020; Karki et al., 2020; Negrini et al., 2021).

A unique feature of COVID-19 seems to be that the length of ICU admission is relatively long and often invasive mechanical ventilation is used (Grasselli et al., 2020). The kind of respiratory support patients receive during ICU admission is of significant relevance to the severity of cognitive deficits shown at hospital discharge and at a one month follow up (Alemanno et al., 2021). As mentioned before, mechanical ventilation is not the only factor that could be of influence on the course of cognitive impairment after COVID-19. Factors such as the occurrence of PICS and its influence on the prevalence of depression, anxiety and PTSD, could also be taken into account. However, as our results suggest length of ICU admission does not influence global cognitive functioning over time, it seems that the influence these factors may be over exaggerated in COVID-19. As ICU admission time is relatively long for COVID-19 (Grasselli et al., 2020), it may be that the effects of PICS are not as influential on cognitive function after a longer period of time in the ICU. More research should be done to investigate if PICS is often prevalent in COVID-19 survivors who got admitted to the ICU and how a longer ICU admission time influences the effects of PICS.

Furthermore, the relationship between the choice of respiratory support systems for patients who suffer from COVID-19 and following cognitive deficits should be investigated more in future research.

4.1 Strengths and Limitations

The strength of this research lies in the focus on the specific patient group who received clinical rehabilitation after COVID-19. We zoomed in on a population neither the CO-FLOW study, nor other Dutch studies have yet focused on. As this research is based on the CO-FLOW study, one of the Dutch authorities in research on the long-term effects of COVID-19, we were able to use their existing knowledge and resources to focus on a small, but very important, patient group. This patient group is very vulnerable, which is why it is important to examine how COVID-19 influences their cognitive function. This knowledge is of major importance to optimize the course of preventive treatment and aftercare for future patients to keep the cognitive damage to a minimum. In addition, data on cognitive ability has been collected with a clear focus on highly used clinical tests, making results objective and reliable.

However, this study has several limitations. Of the 46 participants who were included, no participants received the MoCA at all given timepoints and received all specific cognitive testing. Only 14 participants received the MoCA more than once and the timepoints at which the MoCA was administered differed a lot between participants. A control group of patients who did not suffer from COVID-19 is not included, which makes interpretation of outcomes difficult.

In addition, the linear mixed model fit was poor. Missing data was present for a varying amount of people at every measurement moment, possibly making the data Missing Completely at Random (MCAR), meaning there was no predictable pattern in the data. This may have caused the used model to use biased maximum likelihood data to predict missing values (Carpenter et al., 2021).

One problem that could have caused the amount of missing data could be the fact that in the original CO-FLOW data collection plan, only people with a previous MoCA score <26 were eligible to take the MoCA again. During data collection, this plan was not always followed, resulting in people taking the MoCA even when their previous score was >26. Furthermore, for some participants follow-up measurements data simply had not been performed yet or had not been added to the database yet, at the time this research was conducted.

A follow-up after 1 year and 2 years including more participants as part of the CO-FLOW study is currently underway to allow us to assess possible long-term cognitive deficits using the MoCA.

4.2 Conclusion

Our study focused on the long-term cognitive effects of COVID-19 in patients who received clinical rehabilitation. In summary, this study showed that cognitive impairment is present at rehabilitation center admission in the cognitive domains of complex attention, executive functioning and learning and memory. Severe cognitive impairment was mostly observed in the cognitive domain of complex attention.

Furthermore, we demonstrated that general cognitive functioning improves in the period from rehabilitation center discharge to 3 months post hospital discharge in a group of the same 4 COVID-19 patients. In another group consisting of COVID-19 patients, who were measured once at any of the timepoints, making a within subjects comparison impossible, general cognitive functioning decreases in the period from 3 months post hospital discharge to 6 months post hospital discharge. This outcome opposes existing literature, stating cognitive performance after COVID-19 keeps improving over time. Our results suggest that the course of cognitive function after COVID-19 over time may not be as predictable as we think. More research should be devoted to investigating why the course of cognitive functioning may fluctuate over time and what other factors unique to COVID-19 may contribute to this fluctuation.

We found no relationship between the length of ICU admission related to general cognitive performance at rehabilitation discharge and general cognitive performance over the course of 6 months. These results oppose existing literature. Previous research suggests that factors such as mechanical ventilation and the occurrence of PICS and its influence on the prevalence of depression, anxiety and PTSD, could also be taken into account. However, it seems the influence these factors may be over exaggerated in COVID-19. COVID-19 is characterized by a relatively long ICU admission time. It may be that the effects of PICS are not as influential on cognitive function after a longer period of time in the ICU. As this topic was not the main focus of this study, more research should be done to investigate if PICS is often prevalent in COVID-19 survivors who got admitted to the ICU and how a longer ICU admission time influences the effects of PICS, as well as the influence of different times of mechanical ventilation on cognitive function in COVID-19.

This research contributes to characterizing the course of the cognitive aftermath of COVID-19 in still the early stages of the disease. This may be valuable to predict severity of cognitive deficits in the months following the disease and play a role in optimizing future course of treatment.

This study has focused on a limited number of predictors of the cognitive trajectory of the disease. Upcoming research should focus on other factors such as prevalence of PICS and type of mechanical ventilation that may be of influence on the course of cognitive function after the disease, or on the contrary, may be of less influence than we might expect. Furthermore, future research should focus on following the course of cognitive change in the same people over time, as the measurements in this research were not competed in all participants at the time this study was conducted. In addition, cognitive tests measuring the specific cognitive domains should be administered at multiple timepoints instead of just one. This way, the individual course of cognitive fluctuation in more specific cognitive domains can be observed over time, making it possible to create an even better understanding of how to alter treatment in the right way to reduce the cognitive damage COVID-19 causes to a minimum and save as many lives as possible.

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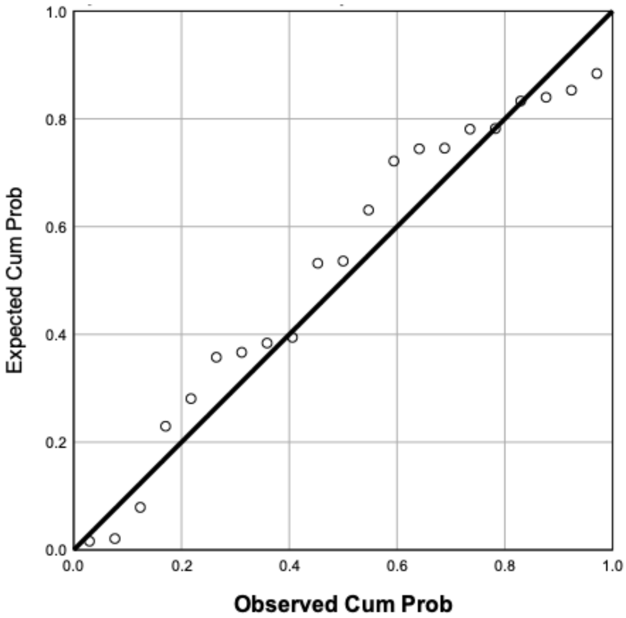
Appendix A

Normal P-P Plot of Regression Standardized Residual. Dependent variable: MoCA score at rehabilitation discharge.



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