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Evaluation of Cognitive Status in Patients With and Without Previous Coronavirus Disease 2019 Infection

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Abstract

Objective: The aim of the study was to assess subjective cognitive function using the validated Cognitive Failures Questionnaire (CFQ) in patients with and without previous coronavirus disease 2019 (COVID-19) infection who presented to Afyonkarahisar Health Sciences University during COVID-19 pandemics.

Methods: This study was conducted at Afyonkarahisar Health Sciences University between October 15, 2022, and November 15, 2022. In our study, the cognitive status of participants was assessed using the CFQ. The sample size was determined as 20-folds of the number of items in the CFQ.

Results: Overall, 525 subjects were recruited to the study including 261 subjects with previous COVID-19 infection (49.7%) and 264 subjects without previous COVID-19 infection (50.2%). The mean CFQ score was 39.42 ± 16.3 and 30.05 ± 14.8 in the subjects with and without previous COVID-19 infection, respectively. The CFQ score was found to be high in 105 (40.2%) of the subjects with previous COVID-19 infection and in 47 (17.8%) of subjects without previous COVID-19 infection. The mean CFQ score was 33.99 ± 13.4 in subjects with mild disease, 49.31 ± 14.8 in those with moderate disease, and 57.82 ± 15.4 in those with severe disease.

Conclusion: Our results indicate that the COVID-19 infection had influence on cognitive status and that there was an association between disease severity and cognitive status. This study is important regarding raising awareness that COVID-19 survivors may experience problems in attention, memory, and clear thinking and emphasizing that there is need for systematic cognitive screening after the recovery of COVID-19.

Keywords: Pandemics, COVID-19, Cognitive Failures Questionnaire

Introduction

Many studies were performed to understand coronavirus disease 2019 (COVID-19) infection during pandemics, and it seemed that they revealed only the tip of the iceberg. In many organ systems, sequels have been observed following COVID-19 infection. Neurological symptoms such as slow thinking, difficulties in focusing, confusion, concentration problems, or memory impairment have been increasingly reported after COVID-19 infection.[1] This perceived mental fatigue and experience have been termed "brain fog" and described in patients with chronic fatigue syndrome.[2] During pandemics, similar symptoms were reported 2 or 3 months after onset of disease in patients who had COVID-19 infection.[3] It has been shown that neuronal damage caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might have long-term adverse effects on cognitive functions, daily living, and quality of life.[4] Accordingly, several reports showed that majority of patients experienced persistent cognitive problems with memory impairment and disruption in the ability to concentrate for months after recovery from COVID-19 disease. In a large USA survey including more than 1500 participants with a previous COVID-19 infection, it was found that >50% of the patients experienced problems in concentration and focusing which was the fourth leading long-term symptom following COVID-19.[5] Persistent attention deficit was observed in a study on 29 middle-aged patients recovered from COVID-19 disease, while executive dysfunction was found 2-3 months after discharge in a study including 58 patients.[6,7] In a study from UK, an internet-based cognitive test was employed to assess cognitive functions in 84 285 cases with suspected or confirmed COVID-19 after recovery, revealing a wide spectrum of cognitive impairment in memory, attention, and executive functions.[8] In that study, cognitive disorders were more prominent in hospitalized cases; more importantly, it was shown that cognitive dysfunction was also observed in patients who were treated at outpatient settings and those without respiratory distress.[8] In this study, we aimed to investigate problems in attention, memory, and clear thinking in patients recovered from COVID-19 and to raise awareness in this issue.

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Methods

Participants

This study was conducted at Afyonkarahisar Health Sciences University between October 15, 2022, and November 15, 2022. The study included male and female volunteers (aged 18-65 years) who had positive result in COVID-19 reverse transcription polymerase chain reaction test, which returned to negative. Based on the National Institute of Health criteria, disease severity was defined as mild, moderate, and severe based on history. In addition, healthy male and female volunteers (aged 18-65 years)

without history of COVID-19 disease were included in the study as controls. Patients with dementia or psychiatric disease were excluded. The sample size was determined as 20-folds of the number of items in Cognitive Failures Questionnaire (CFQ).[9]

Survey form

The survey form included 8 parameters regarding sociodemographic data and COVID-19 characteristics. The CFQ includes 25 items rated with a 5-point Likert scale. The CFQ is widely used to measure general cognitive failures. It is associated to daily memory failures, which is used as a self-reported measurement of mental delay. The CFQ was developed to assess frequency of failures due to cognitive status by Broadbendt[10] in 1982. It includes 25 items rated as follows: 4, very often; 3, quite often; 2, occasionally; 1, very rarely; and 0, never. The total score is estimated by individual item scores and ranges from 0 to 100. Higher scores indicate increased tendency for cognitive failure. The CFQ was proven as a reliable and valid tool.[11] In addition, total score ≥ 43 is defined as high CFQ score. In a factor analysis study from USA, the usefulness of total score as an index for general cognitive failure and 4 subscales for specific cognitive failure domains were confirmed.[12] The subscales include memory (7 items, range: 0-28), distractibility (9 items, range: 0-36), blunders (7 items, range: 0-28), and names (2 items, range: 0-8).

Ethical Approval

The study was approved by Ethics Committee on Clinical Research of Afyonkarahisar Health Sciences University Health Sciences University (approval date: October 7, 2022; number: 2022/12). The study was conducted in accordance to the tenets of Helsinki Declaration. The Strengthening the Reporting of Observational Studies in Epidemiology reporting criteria were followed in the study.

Statistical Analysis

Frequency, percent, arithmetic mean, and SD were used as descriptive statistics in the study. Categorical data were analyzed using the Pearson's chi-square test. For quantitative data, the Mann–Whitney *U*-test was used for binary comparisons, whereas the Kruskal–Wallis test was used for comparisons between ≥3 groups. Data distribution was assessed using the Shapiro–Wilk test. A *P*-value < .05 was considered as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).

Results

Overall, 525 subjects were recruited to the study including 261 subjects with a history of COVID-19 infection (49.7%) and 264 subjects without previous COVID-19 infection (50.2%). The mean age was 40.05 ± 14.5 years in the study population, while it was 42.52 ± 14.6 years and 37.61 ± 14.06 in the subjects with and without previous COVID-19 infection, respectively. Of the subjects, 235 (44.8%) were male and 290 (55.2%) were female. Of the subjects with previous COVID-19 infection, 148 (56.7%) were female and 113 (43.3%) were male. Again, of the subjects without previous COVID-19 infection, 142 (53.8%) were female and 122 (46.2%) were male. There was no significant difference between female and male subjects regarding history of COVID-19 infection (*P* = .280). There was a history of chronic disease in 122 (42.9%) of subjects with previous COVID-19 infection and in 69 (26.1%) of subjects without previous COVID-19 infection. The history of chronic disease was significantly more common in subjects with previous COVID-19 infection (*P* < .0001). Table 1 summarizes demographic characteristics of the participants. There was no significant correlation between disease severity and gender (*P* = .303). However, there was a significant correlation between disease severity and presence of

Table 1. Characteristics of Participants

Characteristics	COVID-19 N (%)	Control N (%)	*P*
Sex			
Female	148 (56.7)	142 (53.8)	.280
Male	113 (43.3)	146 (46.2)	
Comorbidities			
Yes	112 (42.9)	69 (26.1)	<.0001
No	149 (57.1)	195 (73.9)	

Table 2. Disease Severity in Subjects with Previous COVID-19 Infection

	Gender		Chronic Disease	
Disease Severity	Female N = 148	Male N = 113	Yes	No
Mild	109 (59.2)	75 (40.8)	55 (29.9)	129 (70.1)
Moderate	23 (46.9)	26 (53.1)	34 (69.4)	15 (30.6)
Severe	16 (57.1)	12 (42.9)	23 (82.1)	5 (17.9)
P	.303		<.0001	

Table 3. Cognitive Failures Questionnaire Scores

Score	Control (n = 264)	COVID-19 (n = 261)	*P*	Mild (n = 184)	Moderate (n = 49)	Severe COVID-19 (n = 28)	*P*
CFQ total score	30.05 ± 14.8	39.42 ± 16.3	.003	33.99 ± 13.4	49.31 ± 14.8	57.82 ± 15.48	<.0001
Memory	6.99 ± 4.7	9.12 ± 5.5	<.0001	7.34 ± 4.3	11.76 ± 5.5	16.18 ± 5.3	<.0001
Distractibility	11.93 ± 6.0	16.72 ± 7.2	<.0001	14.54 ± 6.2	20.96 ± 6.7	23.64 ± 7.3	<.0001
Blunders	7.98 ± 4.1	10.00 ± 4.6	<.0001	8.91 ± 4.2	12.31 ± 4.4	13.18 ± 4.2	<.0001
Names	3.13 ± 2.3	3.57 ± 2.1	.010	3.20 ± 2.0	4.29 ± 2.0	4.82 ± 1.82	<.0001

CFQ, Cognitive Failures Questionnaire; COVID-19, coronavirus disease 2019.

Table 4. Time from Coronavirus Disease 2019 Infection and Cognitive Failures Questionnaire Scores

Score	0-6 Months (n = 93)	6-12 Months (n = 112)	12-24 Months (n = 46)	>24 Months (n = 10)	*P*
CFQ total score (0-100)	47.13 ± 17.1	35.19 ± 14.6	35.54 ± 12.9	33.00 ± 16.9	<.0001
Memory (0-28)	11.09 ± 6.6	8.19 ± 4.6	7.78 ± 4.1	4.40 ± 5.1	.008
Distractibility (0-36)	20.22 ± 6.9	14.95 ± 6.9	14.43 ± 5.8	14.70 ± 8.5	<.0001
Blunders (0-28)	11.84 ± 4.1	8.70 ± 4.3	9.98 ± 4.4	7.70 ± 4.2	<.0001
Names (0-8)	3.99 ± 2.1	3.36 ± 2.1	3.35 ± 2.1	3.20 ± 2.5	.148

CFQ, Cognitive Failures Questionnaire.

chronic disease ($P < .0001$). Table 2 summarizes the correlation between disease severity and gender or chronic diseases. Of the subjects with previous COVID-19 infection, 93 (35.6%) had COVID-19 infection within prior 6 months, whereas 112 (42.9%) had COVID-19 infection 6 months-1 year ago, 46 (17.6%) had COVID-19 infection 1-2 years ago, and 10 had COVID-19 infection >24 months ago. Of the subjects with previous COVID-19 infection, 184 (70.5%) had mild COVID-19 disease, while 49 (18.8%) had moderate COVID-19 disease and 28 (10.7%) had severe COVID-19 disease. The mean CFQ score was 39.42 ± 16.3 and 30.05 ± 14.8 in the subjects with and without previous COVID-19 infection, respectively. The mean CFQ score was significantly higher in subjects with previous COVID-19 infection ($P = .003$). The all subscales of CFQ (memory, distractibility, blunders, and names) were significantly poorer in subjects with previous COVID-19 infection ($P < .0001$, $P = .001$, $P > .0001$, $P < .0001$).

Table 3 summarizes CFQ scores. The mean CFQ score was 33.99 ± 13.4 in subjects with mild disease, 49.31 ± 14.8 in those with moderate disease, and 57.82 ± 15.4 in those with severe disease. There was a significant correlation between disease severity and worsening in cognitive status ($P < .0001$). Table 4 summarizes the correlation between CFQ score and time from disease onset. It was found that the CFQ score was high in 105 (40.2%) of the subjects with previous COVID-19 infection and 47 (17.8%) of subjects without previous COVID-19 infection. The high CFQ score prevalence was significantly higher in subjects with previous COVID-19 infection ($P < .0001$). The mean CFQ score was found to be significantly higher in subjects with COVID-19 disease within prior 6 months ($P < .0001$). Table 5 summarizes correlations between high CFQ score and gender, chronic disease, COVID-19 infection, disease severity, and time from disease onset.

Discussion

In this study, we demonstrated that subjective cognitive failure was more common in patients with a history of previous COVID-19 infection. The World Health Organization (WHO) has emphasized that patients having COVID-19 infection may experience problems in attention, memory, and clear thinking.[13] In a French study on 120 patients hospitalized due to COVID-19 disease, it was reported that 34% experienced amnesia, while 27% experienced attention deficit after several months; however, authors reported a significant difference between patients admitted to ward or intensive care unit (ICU).[14] In our study, we observed that cognitive failures persisted several months after COVID-19 infection, but cognitive failure was more common in patients with severe disease. A study from UK study including 84 285 subjects revealed cognitive impairment in memory, attention, and executive functions; however, the study did not report the time to cognitive tests from the COVID-19 diagnosis.[8] In our study, patients were stratified by time from COVID-19 infection. In another study from the UK, it was reported that there was a new or worsening concentration problem in 16.2% of patients admitted to the ward and 34.4% of ICU patients.[15] Similarly, new or worsening problems in short-term memory were reported in 17.6% of patients admitted to ward and 18.8% of ICU patients. In our study, CFQ scores were found to be higher in subjects with a history of severe disease. In a study on symptoms of long COVID syndrome, it was reported that cognitive dysfunction started within first week of infection; it progressively worsened within first 3 months and it gradually recovered thereafter.[16] In our study, the mean CFQ

Table 5. High Cognitive Failures Questionnaire Scores

Characteristics	CFQ > 43	CFQ < 43	*P*
Sex			
Female	104 (68.4%)	186 (49.9%)	<.0001
Male	48 (31.6%)	187 (50.1%)	
Comorbidities			
Yes	68 (44.7%)	84 (55.3%)	.002
No	113 (30.3%)	260 (69.7%)	
COVID-19 infection			
Yes	105 (40.2%)	156 (59.8%)	<.0001
No	47 (17.8%)	217 (82.2%)	
Time from COVID-19 infection			
0-6 months	55 (59.1%)	38 (40.9%)	<.0001
6-12 months	35 (31.2%)	77 (68.8%)	
12-24 months	13 (28.3%)	33 (71.7%)	
>24 months	2 (20%)	8 (80.0%)	
Disease severity			
Mild	46 (25%)	138 (75.0%)	<.0001
Moderate	34 (69.4%)	15 (30.6%)	
Severe	25 (89.3%)	3 (10.7%)	

CFQ, Cognitive Failures Questionnaire; COVID-19, coronavirus disease 2019.

score was significantly higher in subjects with COVID-19 infection within prior 6 months. The cognitive failure observed following COVID-19 infection may be due to "persistent activation of immunity" or posttraumatic stress disorder[17] In addition, hypoxemia, hypercoagulability, and neuro-inflammation may also lead to neurocognitive regression in such patients.[18] It has also been proposed that SARS-Cov-2 may have direct access to brain through a wide organotropism in kidneys, liver, and heart.[19] However, it failed to detect virus in the cerebrospinal fluid samples in the majority of patients with encephalopathy during COVID-19 infection; in addition, it was also failed to demonstrate direct viral invasion to brain neuropathological studies.[20,21] In a study on 29 cases with subacute COVID-19 infection, neurological symptoms, and abnormal findings on brain magnetic resonance imaging, 8F-fluorodeoxyglucose positron emission tomography (18FDG) PET scan showed frontoparietal hypometabolism in association with severity of cognitive disorder in the majority of the patients. In particular, marked microglia activation was observed within white matter without irreversible cortical damage, preserving cortical gray matter. These data suggest the presence of neocortical dysfunction, at least in patients hospitalized with subacute COVID-19 disease, and may be translated as cognitive impairment as a result of diffuse white matter and brainstem pathology rather than cortical damage due to direct viral invasion.[22]

A potential confounder is the fact that the patients with prolonged ICU stay due to critical illness are already at risk for long-term cognitive impairment, poorer general cognition, and executive function score.[23]

The study has some strengths, such as using face-to-face interviews to collect data, taking time from COVID-19 infection into consideration, and classifying disease severity according to the WHO criteria. The study also has some limitations. First, it is unclear whether cognitive failure symptoms are specific to COVID-19 or represent a general cognitive disorder related to ICU care. Second, it is also unknown whether subjects without previous COVID-19 had a symptomatic infection. In conclusion, it was observed that cognitive failure was more common in patients with a previous history of COVID-19 infection. Future studies to confirm the specific cognitive effects and pathophysiology of COVID-19 will be guiding in this regard.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee on Clinical Research of Afyonkarahisar Health Sciences University (Approval no: 2022/12, Date: October 7, 2022).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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