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Evaluation of cognitive functions and dementia two years after COVID-19 infection

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Abstract

Background: The Coronavirus disease 2019 (COVID-19) causes high morbidity and mortality in the acute period. Some patients with COVID-19 continue to have symptoms for a long time. However, data on the long-term effects of COVID-19, particularly on cognitive disorders is scarce. We aimed to evaluate cognitive functions and dementia in patients who survived two years after discharge from hospital due to acute covid-19 infection. *Methods:* Two hundred and five patients who had neurological symptoms during index hospitalization for COVID-19 infection were evaluated two years after discharge, and 64 patients were included in the study. According to cognitive assessments, patients were grouped as having normal cognitive levels (48 patients) or impaired cognitive levels (16 patients). *Results:* The impaired cognitive level was found in 16 (25.0%) of patients who underwent cognitive tests. Age, the pre-existence of neurological comorbidity, mean intensive care unit day, and Beck's Anxiety Inventory and Beck's Depression Inventory scores in the impaired cognitive level group were significantly higher than the normal cognitive level group (p:0.001, p:0.013, p:0.015, p:0.004 and p:0.008). The frequency of cognitive impairment in patients who developed altered mental state during hospitalization was 36.0%, while it was 17.9% in patients with normal mental state. Age, the pre-existence of neurological comorbidity, and anxiety were determined as independent risk factors for impaired cognitive level. In addition, we detected new-onset dementia in 8 patients (12.5%). *Conclusion:* We found a high frequency of cognitive impairment and new-onset dementia among COVID-19 survivors who developed neurological manifestations during the acute infection phase.

Keywords: COVID-19, altered mental state, cognitive decline, dementia

INTRODUCTION

Within just two years, the coronavirus disease 2019 (COVID-19) has turned into a huge problem affecting the whole world in many aspects, especially in health-related issues. Many studies have shown that COVID-19 leads to high morbidity and mortality.[1,2]

COVID-19 patients are at high risk of developing neurological complications.[3] COVID-19 may affect the central nervous system (CNS) through one or a combination of different pathways, such as direct injury of nerve cells, systemic inflammation, peripheral organ dysfunction, cerebrovascular changes, and metabolic disorders.[1,3,4] In the acute phase, COVID-19 can cause a wide spectrum of neurological symptoms ranging from headache, fatigue, loss of taste and smell, altered mental status, seizure, ischemic and hemorrhagic stroke.[5,6]

Cognitive impairments such as memory loss, slowed thoughts, concentration problems, difficulty in orientation to place and time, difficulty in problem solving and word finding difficulty have been reported frequently in COVID-19 survivors in the long term.[7,8] While most studies demonstrating neurocognitive decline have evaluated the first six months after acute infection[9–11], only a handful of studies presented up to one year of data.[12,13] Similarly, only a few studies have addressed new-onset dementia after COVID-19.[14,15] While most of these studies reported that cognitive disorders caused by COVID-19 persist for a long time[9–11,16], one study emphasized that cognitive impairment associated with COVID-19 spontaneously

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resolves after one year.[12] Most of these articles highlighted the need for long-term longitudinal studies to evaluate the true impact of COVID-19 on cognitive dysfunction and dementia.[9,10,14] There is insufficient data on when would the decline in cognitive functions return to normal.

In this study, we primarily aimed to evaluate cognitive functions in patients who survived two years after discharge from hospital due to acute COVID-19 infection; and secondly, to detect newly diagnosed dementia, and thirdly to determine whether newly detected cognitive disorders were related to mental status changes that developed during hospitalization.

METHODS

This study was conducted at Ankara Bilkent City Hospital, a tertiary care academic center. Three hundred-seven patients for whom neurology consultation was requested due to new neurological complaints and symptoms developed while being followed up in the COVID-19 intensive care units (ICU) and wards between April 2020 and September 2020 were evaluated. Sixty-four patients who were eligible for cognitive assessment tests were included in the study (Figure1).

The neurological examinations and cognitive tests of the patients were performed by two neurologists experienced in dementia. The mini-mental state examination (MMSE) and the frontal assessment battery (FAB) tests were applied to the patients as cognitive assessment tests. The MMSE test was applied to the patients according to their education level. An MMSE test score below 24 was considered an impaired cognitive level.[17] According to the MMSE assessment, patients were grouped into those with normal cognitive levels (MMSE score ≥24) and those with impaired cognitive levels (MMSE score < 24). Additionally, Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI), the Posttraumatic Stress Disorder Scale (PTSDS), and the Fatigue Severity Scale (FSS) were obtained.

Patient data were recorded, including medical history, current neurological complaints, pre-existing comorbid diseases, clinical course,

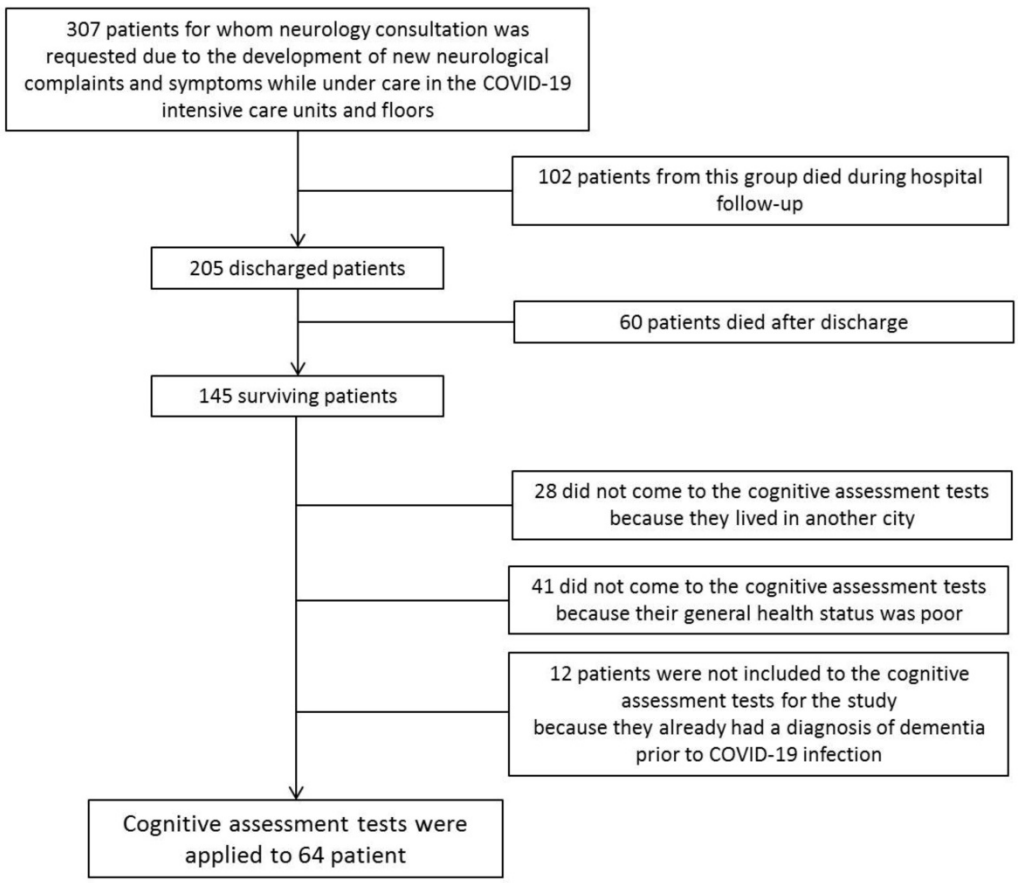

Figure1. Flow chart of the study group

laboratory data, and radiographic studies during hospital follow-up.

In order to determine the effect of the patients' consciousness state during the hospitalization on cognitive functions in the long term, patients were divided into two groups, altered mental state (AMS) and normal mental state (NMS), according to their neurological examinations at the hospitalization (two years ago). If the patient's level of consciousness and interaction with the environment was normal, this was defined as NMS. If somnolence, agitation, delirium, confusion, and coma were present, this condition was defined as AMS.

The study was approved by the local ethical committee (Ankara City Hospital Ethics Committee).

All statistical analyses were done using IBM SPSS statistic 22.0 (Chicago, IL, USA). The data were expressed as mean ± SD. The Mann-Whitney U test or Student's t-test was used to compare the continuous variables, depending on the parametric or non-parametric distribution. Categorical variables were compared using the Chi-Square test. Binary logistic regression analysis was performed to detect independent factors associated with impaired cognitive level. A p-value < 0.05 was considered statistically significant.

RESULTS

Normal cognitive level versus impaired cognitive level

While impaired cognitive level (MMSE score < 24) was detected in 16 of the patients, normal cognitive level (MMSE score ≥24) was found in 48 of them.

Demographic, clinical and radiological data at the time of hospitalization

Impaired cognitive level and normal cognitive level groups were similar in terms of gender, positive RT-PCR for SARS-CoV-2, and the number of patients requiring intensive care (p:0.882, p:0.295, and p:0.999). However, the mean ICU day in the impaired cognitive level group was higher than in the normal (p:0.015) (Table1).

Both groups were similar in terms of brain imaging and chest CT findings (Table1).

The frequency of having "at least one medical comorbidity" and "at least one neurological comorbidity" in the impaired cognitive level group was higher than in the normal cognitive level group (p:0.033 and p:0.013) (Table1).

IL-6 levels were higher in the impaired cognitive level group than in the normal cognitive level group (p:0.016). However, CRP, WBC, D-Dimer, hemoglobin, and GFR levels were similar in both groups (Table1).

Cognitive assessment results and psychiatric scales at the end of the second year

The mean age in the impaired cognitive level group was higher than the normal cognitive level group (p:0.001). The mean follow-up time after discharge was similar in the two groups (Table1).

MMSE and FAB scores were lower in the impaired cognitive level group than the normal cognitive level group (for both, p:0.001), whereas FSS and PTSD scores were higher (p:0.027 and p:0.031). BAI and BDI scores in the impaired cognitive level group were significantly higher than the normal cognitive level group (p:0.004 and 0.008) (Table1).

In binary logistic regression analysis, age and the existence of neurological comorbidity and anxiety were determined as independent risk factors for impaired cognitive level after discharge.

The comparison of the groups in terms of current cognitive complaints is presented in Table1.

Comparison of cognitive and psychiatric assessment results at the end of the second year of discharge in patients presenting with AMS and NMS during hospitalization

In their follow-up at the hospital two years ago, 25 patients had AMS, and 39 patients had NMS.

Patients presenting with AMS and NMS were similar in terms of mean age and gender (p:0.197 and p:0.515) (Table2).

While MMSE and FAB scores were lower in the patients presenting with AMS than those with NMS, the difference was significant only for MMSE (p: 0.021). FSS scores were higher in the patients presenting with AMS than in the patients with NMS (p:0.005). PTSD scores were similar in both groups (p:0.247). BAI and BDI scores in the patients presenting with AMS were higher than the patients with NMS (p:0.027 and 0.010) (Table2).

The number of patients with an impaired cognitive level and new-onset dementia after discharge was higher in the patients presenting with AMS than those with NMS, but the differences were not statistically significant (Table 2).

Table 1: Comparison of the patients with normal cognitive level and impaired cognitive level at the end of the second year of discharge

A. Cognitive and psychiatric assessment results

	Normal cognitive level *n*=48	**Impaired cognitive level *n*=16**	***p***
Age (year)	53.04±14.59	67.50±11.46	**0.001**
Gender			
Female	19 (39.6%)	6 (37.5%)	0.882
Male	29 (60.4%)	10 (62.5%)	
Follow-up time after discharge (month)	25.31±1.11	24.81±1.10	0.125
A- Baseline data at the hospitalization period			
Requirement of intensive care unit	18 (37.5%)	6 (37.5%)	0.999
Intensive care unit day	3.45±6.98	11.81±19.95	0.015
Positive RT-PCR for SARS-CoV-2	36 (75%)	14 (87.5%)	0.295
Brain CT/MRI			
No acute changes	33 (73.3%)	9 (56.3%)	0.205
New pathological findings	12 (26.7%)	7 (43.8%)	
Chest CT			
Normal	4 (8.3%)	3 (18.8%)	
Unilateral	10 (20.8%)	2 (12.5%)	0.440
Bilateral	34 (70.8%)	11 (68.8%)	
At least one medical comorbidities	28 (58.3%)	14 (87.5%)	**0.033**
At least one neurological comorbidities	11 (22.9%)	9 (56.3%)	0.013
Laboratory tests			
Glomerular filtration rate	91.47±30.02	85.12±32.09	0.474
White blood cell 10^9/L	7.71±3.04	7.76±3.27	0.955
Hemoglobin g/dL	12.78±2.17	11.98±1.85	0.193
C-reactive protein mg/dL	55.22±54.97	65.12±80.99	0.584
Interleukin-6 pg/mL	22.46±23.66	68.09±94.64	0.016
D-dimer mg/L	1.78±4.07	3.21±6.57	0.332
B- Cognitive assessment results and psychiatric scales at the end of the second year			
MMSE	27.85±1.41	20.01±3.44	**0.001**
FAB	14.77±2.57	8.57±3.27	**0.001**
BDI	14.97±8.58	22.63±7.10	**0.008**
BAI	17.33±13.31	30.18±11.04	**0.004**
FSS	38.45±14.86	47.01±9.67	**0.027**
PTSDS	24.06±15.40	35.72±14.56	**0.031**
Current cognitive complaints			
Memory difficulties	31 (64.6%)	15 (93.8%)	**0.025**
Attention deficit	30 (62.5%)	14 (87.5%)	0.071
Difficulty in finding words	5 (10.4%)	10 (62.5%)	**0.001**
Difficulty in planning	14 (29.2%)	13 (81.3%)	**0.001**
Trouble handling money and bills	11 (22.9%)	13 (81.3%)	**0.001**
Confusion about time and place	15 (31.3%)	11 (68.8%)	**0.008**
Difficulty in handwriting and drawing	5 (10.4%)	9 (56.3%)	**0.001**

CT: Computed tomography, MRI: Magnetic resonance imaging, MMSE: Mini-mental state examination, FAB: Frontal assessment battery, BDI: Beck's Depression Inventory, BAI: Beck's Anxiety Inventory, PTSDS: Posttraumatic Stress Disorder Scale, FSS: Fatigue Severity Scale

Table 2: Comparison of cognitive and psychiatric assessment results at the end of the second year of discharge in patients presenting with NMS and AMS during hospitalization

	NMS *n*=39	AMS *n*=25	*p*
Age (year)	55.38±16.42	58.64±13.03	0.197
Gender			
Female	14 (35.9%)	14 (56.0%)	0.515
Male	25 (64.1%)	11 (44.0%)	
New onset dementia after discharge	3 (7.7%)	5 (20%)	0.146
Patients with impaired cognitive level	7 (17.9%)	9 (36%)	0.104
MMSE	26.79±3.31	24.48±4.62	**0.023**
FAB	14.00±3.12	12.44±4.46	0.110
BDI	14.08±7.54	20.04±9.55	**0.010**
BAI	16.58±13.34	24.65±13.29	**0.027**
PTSD	21.77±13.71	33.63±16.52	0.247
FSS	38.51±13.83	43.12±14.29	**0.005**

AMS: Altered mental state, NMS: Normal mental state, MMSE: Mini-mental state examination, FAB: Frontal assessment battery, BDI: Beck's Depression Inventory, BAI: Beck's Anxiety Inventory, PTSDS: Posttraumatic Stress Disorder Scale, FSS: Fatigue Severity Scale

DISCUSSION

We evaluated moderate-to-severe COVID-19 patients who developed neurological symptoms during hospital follow-up two years after discharge. Our study showed that a significant proportion of survivors developed cognitive decline and new-onset dementia after discharge. Cognitive impairment at the end of the two-year follow-up was detected in 36% of the patients who developed AMS during hospitalization and in 17.9% of the patients with NMS. Eight of the patients with cognitive impairment were also diagnosed with new-onset dementia. Age, pre-existing neurological comorbidity, and anxiety were independent risk factors for cognitive impairment in survivors two years after discharge.

Several studies have shown that some of the symptoms still persist in more than 50% of the patients at the end of the sixth month, especially in hospitalized COVID-19 patients.[18,19] Some studies evaluating up to six months after infection with COVID-19 have reported cognitive impairment in approximately 15-29% of patients.[9,11,20] In another study, Seeßle *et al*. reported that neurocognitive symptoms persist for up to 12 months in approximately 40% of patients.[13] These studies have expressed the need for long-term studies to determine how cognitive disorders will evolve. Brutto *et al*. reported that they detected a cognitive decline in the sixth-month follow-up of the patients, but the cognitive functions recovered spontaneously in the evaluation one year later.[9,12] On the other hand, Poletti *et al*. reported that cognitive impairment was stable in the first, third, and sixth-month follow-ups of the patients following COVID-19.[21] We showed that 25% of patients had impaired cognitive function two years after discharge.

The etiopathogenesis of neurological system involvement in COVID-19 patients is complex and multifaceted. SARS-CoV-2 infection leads to microthrombi and microhemorrhages in the brain. The authors stated that if this micro-pathological process lasts for a long time, it may lead to long-term motor and cognitive impairments through chronic oxidative damage and an increased cellular stress level, especially in elderly patients.[8] We detected intracranial pathology in only 37.5% of our patients with cognitive impairment in neuroimaging during hospitalization. Immune hyperactivation and ongoing excessive inflammation may be another mechanism contributing to neuronal damage in patients recovering from acute COVID-19 infection. IL-6 levels were found to be higher in COVID-19 patients with neurological problems. Moreover, high IL-6 has been associated with intellectual and age-related disability.[22,23] Consistent with these accumulated data, our patients with cognitive impairment had significantly higher IL-6 levels at the time of hospitalization than those with normal cognitive functions.

Up to now, studies have not provided sufficient data on the incidence of post-COVID-19 dementia.[4,8] In a data-based study, Taquet *et al*. reported the frequency of new-onset dementia diagnosis as 2.66% in COVID-19 patients over 65 years of age and 4.72% in patients who developed encephalopathy.[14] We found new-onset dementia in 5 (20%) patients who developed AMS during hospitalization and 3 (7.9%) of those with NMS. The fact that the mean age in our patient population was approximately two decades higher than the patients in the study of Taquet *et al*.[14] may be a reason for the high incidence of dementia in our study. A second reason may be that all of the patients in our study had moderate-to-severe COVID-19 disease.

Recent publications have suggested that the APOE4 allele, the most important gene susceptibility to AD, may play a role in the pathogenesis of AD development in COVID-19 patients, because this allele is also an important risk factor for severe COVID-19.[4,24] Additionally, multiple risk factors shared by these two diseases, such as immune hyperinflammation, cerebral hypoperfusion, age, and pre-existing comorbidities, may accelerate the development of AD in COVID-19 patients.[4,25] However, the precise nature of their connections has not yet been revealed.

It is essential not only for the cognitive disorders brought on by COVID-19 to be diagnosed early but also for effective management methods to be developed against these problems before it is too late. A meta-analysis stated that in elderly patients with mild cognitive impairment, the combined application of cognitive interventions with physical activity was more effective in improving global cognition, memory, executive functions, and attention than the application of cognitive intervention or physical activity alone.[26]

The strengths of our study were as follows; first, it provides data on cognitive functions in the longest follow-up period after discharge in COVID-19 patients. The second is that the study was conducted in a single center, and cognitive and psychiatric test assessments were administered face-to-face. The limitation of our study was that patients did not have basic MMSE tests before the COVID-19 pandemic. Another limitation is that it does not represent the entire population of patients with COVID-19 infection.

In conclusion, our study showed an increased frequency of cognitive impairment and new dementia diagnoses in long-term follow-ups of patients who developed neurological symptoms during COVID-19 infection. The frequency of cognitive disorders was higher, especially in patients who developed altered mental status during hospitalization. Whether this high incidence of dementia was triggered or accelerated by COVID-19 or is part of dementia's natural course, early awareness may enable patients to benefit more effectively from treatment options such as cognitive interventions and physical exercises.

DISCLOSURE

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