

The COVID-19 Related Cognitive Impairments Among Non-Hospitalized and Hospitalized Patients; A Comparative Study

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Abstract

Background: Different patterns and severity of neuropsychological symptoms are reported in patients with COVID-19. The exact pathophysiologic mechanisms responsible for the neuropsychological manifestations of COVID-19 remain unknown. This study aimed to compare the cognitive impairments between hospitalized and non-hospitalized patients with COVID-19.

Methods: This cross-sectional study was performed in a referral hospital in Iran from March 2020 to March 2021. Neuropsychiatric assessments were conducted using the Addenbrooke's Cognitive Examination (ACE) test. Demographic factors, medical history, hospitalization duration, and ACE scores were assessed. Statistical analysis was performed using SPSS.

Results: In this study, 219 patients with COVID-19 (114 hospitalized and 105 non-hospitalized) were evaluated. The mean age of hospitalized patients was significantly higher than that of outpatient participants (48.46 vs. 34.32 years; $P < 0.001$). Gender, handedness, education level, and habitual history did not differ significantly between the two groups. Dexamethasone administration was significantly more common in hospitalized patients. The total and subgroup ACE scores in hospitalized patients were significantly lower than those in the outpatient group. Cognitive impairments were detected significantly more frequently in hospitalized patients. Multivariate analysis showed that cognitive impairments were significantly more common among hospitalized patients ($P < 0.001$).

Conclusions: The cognitive ability of hospitalized patients with COVID-19 is lower than that of their outpatient counterparts regarding executive function, verbal fluency, memory, language, and visual perception. Hospitalized patients with COVID-19 should undergo more detailed neuropsychological evaluations and receive appropriate treatments accordingly.

Keywords: COVID-19; Cognitive Impairments; Hospitalization; Outpatients; Neuropsychiatric test

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) with millions of cases and deaths reminded us how pandemics can affect all aspects of our lives. COVID-19 is mainly known as a disease of the respiratory system; however, evidences have shown that involvement of other organs is probable, including the central and peripheral nervous system, especially in patients with severe forms of the disease [1-3]. Based on reported neurologic manifestations due to the earlier coronavirus-like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [4], neuropsychological involvement has been a rising concern from the beginning of the COVID-19 pandemic [5]. Currently, the number of diagnosed neurologic involvement by COVID-19 infection is rapidly increasing [6,7].

Different patterns and severity of neuropsychological symptoms are reported in patients with COVID-19 and might be persistent even after recovery of the respiratory symptoms [8]. Neuropsychological signs and symptoms were detected ranging from 36.4% to 82.3% in hospitalized COVID-19 cases [9-11]. The most common were anosmia, ageusia, headache, and myalgia [9]. In addition, it was shown that the most frequent cognitive impairments during early and post-acute period were impaired attention, memory, language, and praxis coordination [4,8]. The exact pathophysiologic mechanisms responsible for neuropsychological manifestations of COVID-19 are still unknown [10,11]. It can be due to the direct infection-based effect of virus on central nervous system (CNS), inflammatory immune-mediated disease, or systemic effects of SARS-CoV-2 [12].

Neuropsychological involvement in COVID-19 patients is poorly understood, especially in non-hospitalized patients. In addition, there are some reports indicating persistency of neuropsychological manifestations during post-acute phase [8]. Therefore, cognitive and neuropsychological involvement in COVID-19 patients should be further studied. There may be need for specific intervention and even rehabilitation after acute illness targeting neuropsychological consequences of COVID-19 [8]. This study aimed to compare the cognitive impairments between non-hospitalized and hospitalized COVID-19 patients.

Methods

This cross-sectional study was performed among cases admitted in a referral hospital in Iran, March 2020 to March 2021. Cases with age more than

18 years old and certain diagnosis of COVID-19 were included. Neuropsychological examination and interview by neurosurgery visit (A.P) were done among all patients. The COVID-19 diagnosis was confirmed by infectious disease specialist and pulmonologist according to polymerase chain reaction (PCR) and spiral chest computed tomography (CT) scan. Patients with past history of psychiatric disorder, mild cognitive impairment (MCI), dementia, delirium state, intracranial lesions or surgery, and severe traumatic brain injury were excluded.

Global cognitive state was assessed by the Addenbrooke's Cognitive Examination (ACE) test in all patients and concluded in Persian version. It consisted of six domains consisted of attention, orientation, memory, language, visual perception, and visuospatial skills [13]. Also, the cut-off point was considered as 84; and $ACE \leq 84$ was showed cognitive impairments [13,14].

The variables such as demographic factors, past medical history, hospitalization period, and the results of ACE test were assessed. This study was conducted in accordance with the Declaration of Helsinki and approved by ethics committee of our institution.

Statistical analysis was done using SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; 2016). All quantitative variables were calculated as descriptive statistics. In addition, the chi-square test for categorical variables, and Mann-Whitney U test and Kruskal-Wallis test for inter-group comparison of continuous variables between groups were used. A P-value < 0.05 was calculated significantly.

Results

In this study, 219 COVID-19 patients (114 hospitalized and 105 non-hospitalized) were assessed. The mean age of patients was 41.68 ± 14.11 (range: 18-84 years) and 119 patients (54.33%) were male. The mean age of hospitalized patients was significantly higher than outpatient participants (48.46 vs. 34.32; $P < 0.001$). Gender, handedness, education level, and habitual history were not significantly different between the two groups ($P > 0.05$). Dexamethasone administration was significantly more common in hospitalized patients (48% vs. 4%; $P < 0.001$). The demographic features are shown in table 1.

The mean total score of ACE was 87.74 ± 16.39 . Total and subgroup scores of ACE in hospitalized patients were significantly lower than the outpatient group. Cognitive impairments were more common in hospitalized patients than the other group, which was statistically significant (36.8% vs. 7.6%; $P < 0.001$) (Table 2).

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Table 1: Patient characteristics

Variable			Total	Hospitalized (N=114)	Outpatient (N=105)	p-value
Age			41.68±14.11	48.46 ±13.61	34.32 ±10.54	0.000
Sex	Male		119 (54.3%)	65 (57%)	54 (51.4%)	NS*
	Female		100 (45.7%)	49 (43%)	51 (48.6%)	
Handedness	Left		14 (6.4%)	5 (4.4%)	9 (8.6%)	NS
	Right		205 (93.6%)	109 (95.6%)	96 (91.4%)	
Education	Under diploma		55 (25.1%)	33 (29%)	22 (21%)	NS
	Diploma and more		164 (74.9%)	81 (71%)	83 (79%)	
Smoking	No		186 (84.9%)	97 (85.1%)	89 (84.8%)	NS
	yes		33 (15.1%)	17 (14.9%)	16 (15.2%)	
Alcohol	No		187 (85.4%)	106 (93%)	81 (77.1%)	NS
	yes		32 (14.6%)	8 (7%)	24 (22.9%)	
Opioid	No		216 (98.6%)	112 (98.2%)	104 (99%)	NS
	yes		3 (1.4%)	2 (1.8%)	1 (1%)	
Dexamethasone administration	No		160 (73%)	59 (52%)	101 (96%)	0.001
	Yes		59 (27%)	55 (48%)	4 (%4%)	

* NS = Not Significant (p-value>0.05)

Table 2: The results of ACE test in detail between our participants

Score		Total	Hospitalized	Outpatient	p-value
ACE		87.74±16.39	80.68 ± 19.29	95.41 ± 6.70	0.000
Executive functioning		16.14±2.53	15.17 ± 2.91	17.20 ± 1.42	0.000
Verbal fluency		10.59±3.48	9.01 ± 3.63	12.31 ± 2.31	0.000
Memory		22.32±5.14	20.17 ± 6.11	24.67 ± 2.02	0.000
Language		24.09±3.95	22.74 ± 4.96	25.56 ± 1.34	0.000
Visio Spatial		14.57±3.21	13.56 ± 4.07	15.66 ± 1.12	0.000
Cognitive impairment	Yes	50 (22.8%)	42 (36.8%)	78(7.6%)	0.000
	No	169 (77.2%)	72 (63.2%)	97 (92.4%)	

corticosteroids were confounding factors in this study. Hospitalized patients were significantly older than the outpatient group, and systemic corticosteroids were prescribed more commonly in hospitalized patients. Multivariate analysis was performed to remove the confounding effect, which revealed that cognitive impairments were significantly more common among hospitalized patients (Figures 1 and 2).

Discussion

COVID-19 as a multi-organ disease with many aspects, such as neuropsychiatric problems, is still unknown. Here, we focused on cognitive impairment in non-hospitalized COVID-19 patients compared to hospitalized ones. This study is rather unique in comparison to similar works done so far; the relatively large number of patients studied in the acute stage, as well as studying the neurocognition of outpatients in comparison with hospitalized patients, makes this study noteworthy. Except for age and corticosteroid administration, there was no significant difference in characteristics between inpatient and outpatient

groups. This can be related to the higher risk of admission in older patients; also, systemic steroids were used more commonly in hospitalized patients. Multivariate analysis removed the confounding effect of age and corticosteroid administration. In addition, among hospitalized patients, we did not include those admitted to intensive care units needing mechanical ventilation.

In our study, cognitive function was significantly lower in hospitalized patients compared to outpatients. There is no consensus on the exact definition of cognitive impairments; here we used an ACE score ≤ 84 to define it [13,14]. The prevalence of cognitive impairment among outpatients and hospitalized ones was 6.7% and 36%, respectively. Previous studies have reported neuropsychologic involvement among hospitalized patients with a prevalence ranging from 36.4% to 82.3% [9-11].

Cognitive impairment seems to occur more commonly in the severe form of the disease [9,15-18,19-21]. In our study, patients with critical illness requiring hospitalization experienced more cognitive impairment. It should be noted that cognitive

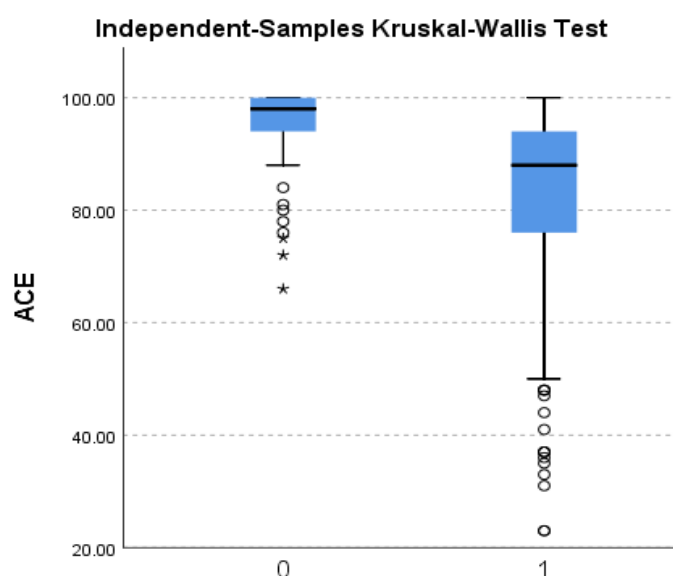


Figure 1: Distribution of ACE test score among non-hospitalized (group 0) and hospitalized patients (group 1)

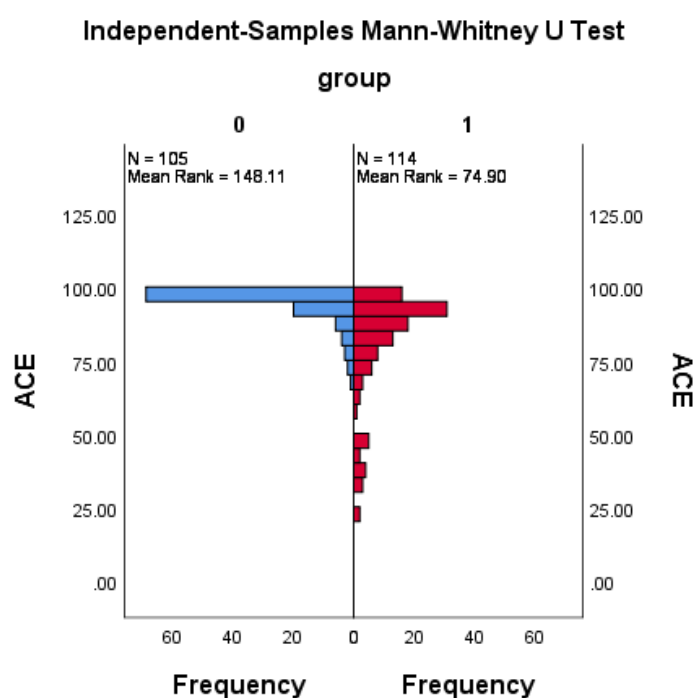


Figure 2: Frequency and distribution of ACE test score among non-hospitalized (group 0) and hospitalized patients (group 1)

impairment was also observed in the outpatient group and there are reports of cognitive decline in non-hospitalized patients without any respiratory difficulty [21]. Considering the more prevalent cognitive dysfunction among hospitalized patients, it is recommended to perform more neuropsychological evaluations for hospitalized patients, especially those admitted to intensive care units.

We studied patients in the acute phase regarding

the fact that neuropsychological manifestations resulting from COVID-19 happen in the second week of the disease initiation [6,9,22-24]; however, some reports have described delayed neurocognitive decline in the post-acute phase even among patients without neurological involvement in the acute stage [21,25,26].

To understand the neuropsychological aspect in hospitalized COVID-19 patients, the systematic

review by Ritchie et al. (2020) is helpful. About 70% of COVID-19 cases who were admitted to intensive care units for mechanical ventilation suffered from cognitive impairment due to acute respiratory distress syndrome (ARDS). Cognitive problems were detected in more than 78% of cases with ARDS one year after hospitalization and 50% after two years [27]. Therefore, when it comes to neuropsychological involvement in COVID-19 patients, it is recommended to consider possible delayed and also residual manifestations after the acute phase.

The profile of cognitive decline due to COVID-19 has been poorly understood. In this study, there was a problem with executive function, verbal fluency, memory, language, and visual perception, and deficits were found to be worse among hospitalized patients in all domains compared to outpatients. This was in concordance with previous studies. Negrini et al. (2021) investigated cognitive functions in nine hospitalized SARS-CoV-2 patients using the Mini-Mental State Examination (MMSE) test. In their study, three patients (33.3%) had impaired cognitive scores in the MMSE, with a specific decline in attention, memory, language, and praxis abilities. The cognitive decline appeared to be directly related to the duration (days) in the intensive care unit (ICU) [8]. Another study by M. Almeria et al. (2020) investigating 35 patients with COVID-19 has found a decline in memory, attention, and executive function among patients presenting with headache, anosmia, dysgeusia, diarrhea, and those who required oxygen therapy compared to asymptomatic patients [28].

Although we examined patients in the acute phase, cognitive impairment in COVID-19 patients might have a delayed presentation in the post-acute stage that needs further studies [21,25,26]. Moreover, a broader understanding of neurocognitive involvement may require regular follow-ups for long periods. Additionally, we examined hospitalized patients without including those admitted to the ICU, while there is evidence of links between ICU admission as well as oxygen therapy with cognitive impairment [8,28].

Conclusion

Cognitive ability of hospitalized COVID-19 patients is lower than outpatient counterparts considering executive function, verbal fluency, memory, language, and visual perception. Hospitalized patients with COVID-19 should undergo more accurate neuropsychological evaluations, and then get appropriate treatments accordingly.

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