Original Article

Prevalence and clinical impact of neurocognitive symptoms in geriatric patients with COVID-19.

Mahmoud Mohamed Lotfy[1], Khalid Elsayed Elsorady [1], Samia Ahmed Abdul-Rahman [1], Mohamed Shawky khater [1]

[1] Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University.

ABSTRACT

Background: Multiple neurocognitive manifestations of COVID-19 have been reported. Symptomatic patients with COVID-19 typically present with respiratory symptoms but neurocognitive symptoms are common, especially in geriatric hospitalized patients with severe infection.

Objective: To determine the prevalence and clinical impact of neurocognitive symptoms on outcome of COVID-19 in geriatric patients.

Patients and methods: A retrospective observational study conducted in Ain- Shams University Geriatrics hospital for isolation of COVID- 19 patients. Number of included patients was 233 patients with positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) results for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection. Length of stay was determined and mortality was the primary clinical outcome. Statistical analyses were performed.

Results: We found that 54% of the studied cases had neurocognitive manifestations. Delirium and decline in conscious level were higher in deceased patients with statistically significant difference. There was significant difference between alive and deceased groups regarding the presence of either neurocognitive or respiratory symptoms. Higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score was significantly associated with higher mortality rate. There was significant differences regarding TLC, serum sodium, Blood Urea Nitrogen (BUN), creatinine, albumin, C - reactive protein (CRP), Ferritin, and D-Dimer. Upon regression analysis higher APACHE II score was an independent risk factor for mortality.

Conclusion: Neurocognitive manifestations were common among hospitalized geriatric patients with COVID-19 and were associated with poor hospital outcomes. Accordingly, these manifestations should be taken seriously and should receive early interventions to prevent undesirable events.

Key words: Neurocognitive symptoms, Delirium, COVID-19, Geriatric patients.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the COVID-19 pandemic, which has resulted in more than 4.8 million confirmed cases and in the deaths of more than 300,000.[1] It is the worst reported pandemic since the 1918 influenza pandemic.[2]

Even though respiratory symptoms are COVID-19's most typical presentation, reports of neurocognitive characteristics are on the rise. These characteristics seem to be a combination of generalized systemic symptoms, the results of a direct viral infection, or inflammation of the neural system, which may be post-infectious or para-infectious. [3]

Similar to Middle East respiratory syndrome and SAR [4,5], Numerous neurological characteristics of COVID-19 have been identified. According to a previous analysis of 214 patients with severe COVID-19, 36% of the patients had neurologic symptoms.[6] Hospitalized COVID-19 patients commonly have a multitude of mild neurological non-specific symptoms, such as headache, fatigue, anorexia, dizziness, muscle discomfort, anosmia, and ageusia[7-9], although the epidemiology may be different in milder conditions.[10-12] Acute cerebrovascular stroke linked to multiple causes may accompany more severe COVID-19 presentations[13,14], and confusion or impaired consciousness.[6,15] Some patients have also been documented to have acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome).[16,17] Additionally, meningoencephalitis and hemorrhagic posterior reversible encephalopathy syndrome[18].[19]

Geriatric individuals frequently appear with unusual symptoms, such as the existence of specific syndromes including altered levels of consciousness, urine incontinence, falls and without a febrile reaction.[20,21] About 20% of elderly patients in emergency rooms had atypical presentations.[22] Delirium can occur throughout the course of COVID-19, but it can also show as one of the symptoms, making diagnosis and treatment difficult, especially in patients with cognitive dysfunction,.[23-27]

Only 20%–30% of elderly people with infections showed up at the emergency rooms feverish. Therefore, looking for other clinical features that predict higher mortality is crucial. The respiratory state of those who are affected has received the majority of attention in the scientific literature about the identification and management of COVID 19. However, mortality from COVID-19 neurological sequelae is highly correlated**.** [28] The prevalence of neurological symptoms including stroke and impaired mental status may be a significant risk factor for death. [29,30] Alteration in mental status and stroke had a higher risk of mortality within the range of central nervous system manifestations than the severity of underlying illness because these syndromes may represent a clinically significant syndromic

expression of SARS-Cov-2 infection.[29] Accordingly, the current study aimed to determine the prevalence and clinical impact of neurocognitive symptoms on outcome of COVID-19 in elderly patients.

PATIENTS AND METHODS

A retrospective observational study conducted in Ain- Shams University Geriatrics hospital for isolation of COVID-19 patients. The study duration was from June 7th 2020 to August 4th 2020. The included cases were 233 patients with positive RT-PCR results for SARS-Cov-2 infection. The inclusion criteria were all geriatric patients 60 years and older, who were admitted with suspected COVID-19 disease and had a confirmed SARS-CoV-2 infection after admission by RT-PCR. The Exclusion criteria were patients with a preexisting mental disorder as psychosis, and patients with preexisting neurocognitive impairment.

Study tools and procedures

All study participants were assessed retrospectively by the following: medical history including socio-demographics, clinical characteristics at admission, and laboratory tests on admission: complete blood count (CBC), C-reactive protein (CRP), D-Dimer, Ferritin, liver function test, kidney function tests. Acute illness severity assessment: Acute Physiology and Chronic Health Evaluation II (APACHE II) score. [31] Length of hospital stay at the hospital was determined and the primary clinical outcome was mortality.

Ethical Considerations

Reviewing and approval of the study protocol by the research review board of the Geriatrics and Gerontology department, and the research ethics committee at the Faculty of Medicine, Ain Shams University (MS 732 / 2021).

Statistical analysis

Statistical Package for Social Science (SPSS), version 26, was used on a personal computer for data entry and statistical analysis. Means and standard deviation were used to present quantitative variables. Frequency tables (number and percent) were used to depict qualitative variables. Comparison between quantitative variables was carried out using Student t test. Using Pearson's 2 test, qualitative variables were compared to one another. Logistic regression analysis was performed for risk factors. Statistical difference was accepted when $P < 0.05$.

RESULTS

In the current study the mean age of participants was 69.69 ± 8.04 years

old with minimum age 60 and maximum age 91. The percentage of male was 49.8% (116) and female was 50.2% (117). The study showed that the percentage of patients with hypertension (HTN) was 63.5%, percentage of patients with diabetes mellitus (DM) was 54.9%, percentage of patients with ischemic heart disease (ISHD) was 23.6%, percentage of patients with chronic kidney disease (CKD) was 14.6%, percentage of patients with cerebrovascular stroke (CVS) was 13.7%, percentage of patients with atrial fibrillation (AF) was 13.7%, percentage of patients with heart failure (HF) was 9.0%, percentage of patients with chronic liver disease (CLD) was 8.6%, percentage of patients with malignancy was 7.3% and percentage of patients with chronic lung disease was 3.9%. There was no statistical significance between alive and deceased groups regarding age and gender. Additionally, it demonstrated that there was no statistically significant difference in terms of comorbidities as described in **Table 1**

Table 1: Demographic and clinical data of participants

Variable		Outcome				t*	P value
		Alive		Deceased			
		Mean	SD	Mean	SD		
Age		69.01	7.91	70.49	8.15	1.40	0.16
		N	%	N	%	X^{2**}	P value
Gender	Male	61	52.6%	55	47.4%	0.21	0.65
	Female	65	55.6%	52	44.4%		
DM	Yes	68	53.1%	60	46.9%	0.11	0.75
	No	58	55.2%	47	44.8%		
HTN	Yes	85	57.4%	63	42.6%	1.84	0.18
	No	41	48.2%	44	51.8%		
ISHD	Yes	31	56.4%	24	43.6%	0.15	0.70
	No	95	53.4%	83	46.6%		
AF	Yes	14	43.8%	18	56.3%	1.59	0.21
	No	112	55.7%	89	44.3%		
HF	Yes	11	52.4%	10	47.6%	0.03	0.87
	No	115	54.2%	97	45.8%		
CLD	Yes	10	50.0%	10	50.0%	0.16	0.69
	No	116	54.7%	96	45.3%		
CKD	Yes	21	61.8%	13	38.2%	0.95	0.33
	No	105	52.8%	94	47.2%		
CVS	Yes	14	43.8%	18	56.3%	1.59	0.21
	No	112	55.7%	89	44.3%		
Chronic lung disease	Yes	7	77.8%	2	22.2%	2.12 FE	0.18
	No	119	53.1%	105	46.9%		
Malignancy	Yes	8	47.1%	9	52.9%	0.36	0.55
	No	118	54.6%	98	45.4%		

*Student t test **Chi square test (FE: Fisher Exact)
Abbreviations: DM: Diabetes Mellitus, HTN: Hypertension, ISHD: Ischemic Heart Disease, AF: Atrial Fibrillation, HF: Heart Failure, CKD: Chronic Kidney Disease, CLD: Chronic Liver Disease, and CVS: Cerebrovascular Stroke.

54% of the studied cases had neurocognitive manifestations on admission.The percentage of neurocognitive symptoms in deceased patients was 53.1% while in alive patients was 46.9% (P-value = 0.02**)** as described in **figure 1**.

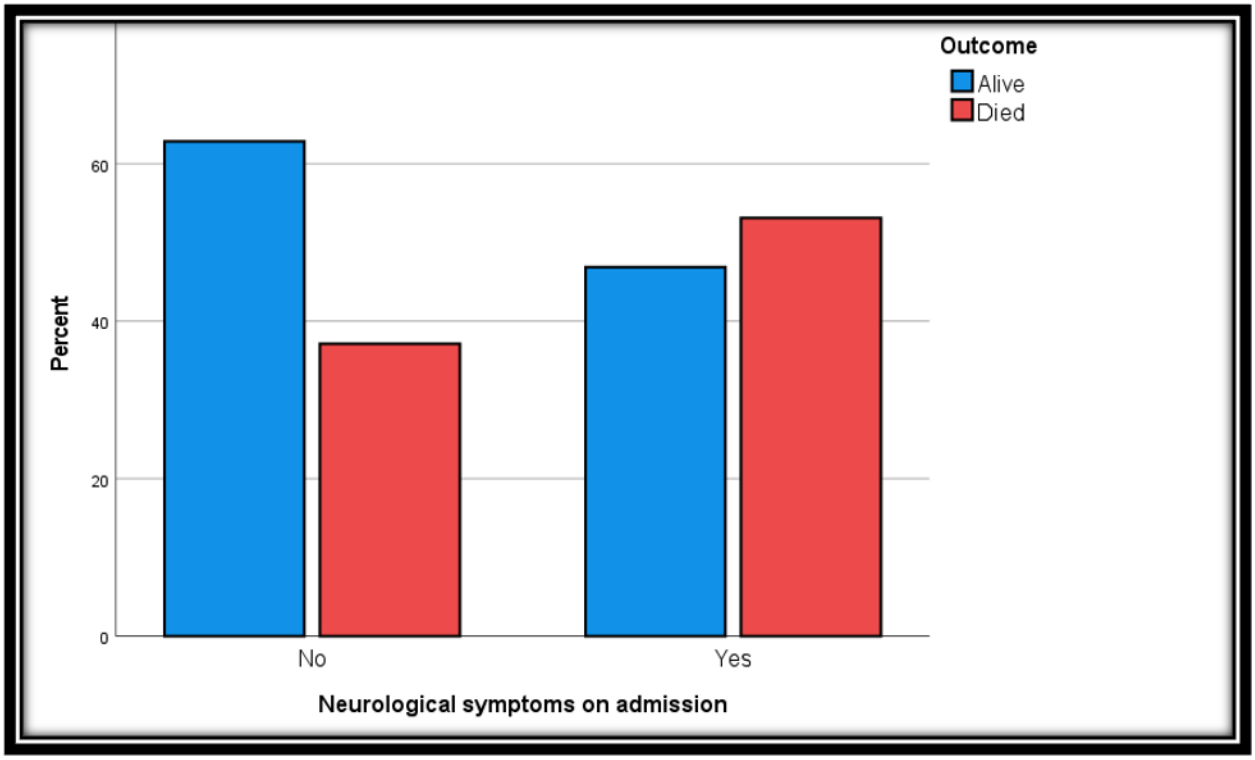

Figure (1) shows that outcomes of neurocognitive symptoms in alive patients and deceased

Delirium and decline in conscious level were more in deceased patients with statistically significant difference (P-value = 0.002). However, there was no statistical difference between alive and deceased groups regarding lateralization, aphasia and generalized tonic-clonic seizures (GTCs). Respiratory distress and hypoxia were more in deceased patients with statistically significant difference, while cough and fever were more in

alive patients with statistically significant difference as described in **Table 2**

Table 2: Neurocognitive and respiratory symptoms on admission

Variable		Outcome				X^{2*}	P value
		Alive		Deceased			
		N	%	N	%		
Neurological symptoms	Yes	60	46.9%	68	53.1%	5.93	**0.02**
	No	66	62.9%	39	37.1%		
Lateralization	Yes	18	45.0%	22	55.0%	1.60	0.21
	No	108	56.0%	85	44.0%		
Aphasia	Yes	5	38.5%	8	61.5%	1.35	0.25
	No	121	55.0%	99	45.0%		
Decline in conscious level & delirium	Yes	31	39.7%	47	60.3%	9.70	**0.002**
	No	95	61.3%	60	38.7%		
GTCs	Yes	18	72.0%	7	28.0%	3.62	0.06
	No	108	51.9%	100	48.1%		
Respiratory symptoms and fever	Yes	89	60.1%	59	39.9%	6.00	**0.01**
	No	37	43.5%	48	56.5%		
Distress	Yes	13	32.5%	27	67.5%	9.05	**0.003**
	No	113	58.5%	80	41.5%		
Hypoxia	Yes	26	43.3%	34	56.7%	3.76	**0.05**
	No	100	57.8%	73	42.2%		
Cough	Yes	37	80.4%	9	19.6%	10.03	**<0.001**
	No	89	47.6%	98	52.4%		
Fever	Yes	41	77.4%	12	22.6%	14.97	**<0.001**
	No	85	47.2%	95	52.8%		

*Chi square test - Bold is significant

Despite overlapping respiratory and neurocognitive symptom of COVID-19 among participants, presence of neurocognitive symptoms on admission was significantly correlated with increased in-hospital mortality (P= 0.02).

Table 3: Association between neurocognitive symptoms and hospital outcomes

		Respiratory symptoms		Neurocognitive symptoms		t*	P value
		Mean	SD	Mean	SD		
Length of Hospital Stay (days)		11.06	6.73	11.70	7.13	0.71	0.48
		N	%	N	%	X^{2*}	
Outcome	Alive	66	62.9%	60	46.9%	5.93	**0.02**
	Died	39	37.1%	68	53.1%		

- Bold is significant
*Student t test *Chi square test

Regarding laboratory results and acute illness severity assessment: mean values of TLC, serum sodium, BUN, creatinine, CRP, ferritin, D-dimer and APACHE 2 score were significantly higher in deceased patients. While serum albumin was significantly lower in deceased patients (P-value <0.001) as described in **Table 4**

Table 4: Laboratory findings and APACHE II score

Variable	Outcome				t*	P value
	Alive		Deceased			
	Mean	SD	Mean	SD		
HB	11.27	2.19	10.83	2.48	1.43	0.16
TLC #	8.30	6.60-11.50	9.60	7.00-15.00	2.13	**0.03**
Platelets	239.40	101.03	214.90	100.70	1.83	0.07
Serum sodium	134.42	6.94	137.65	11.25	2.58	**0.01**
Serum potassium	4.17	.75	4.16	.86	0.08	0.94
BUN	35.01	24.40	52.75	35.73	4.29	**<0.001**
Serum creatinine #	1.20	.90-1.90	1.60	1.00-3.20	2.64	**0.01**
Serum alanine transaminase #	23.00	16.00-39.00	21.00	16.00-37.00	0.37	0.72
Serum albumin	3.31	.50	3.03	.62	3.73	**<0.001**
Serum CRP #	56.00	31.00-97.00	105.00	32.00-217.00	3.08	**0.002**
Serum ferritin #	526.00	287.00-906.00	930.00	670.00-1650.00	4.46	**<0.001**
Serum D-Dimer #	1.20	.70-2.30	2.00	1.00-3.80	2.32	**0.02**
APACHE II score	9.46	3.86	13.92	5.27	4.15	**<0.001**

#Median and IQR (Mann Whitney U test) *Student t test - Bold is significant

Length of hospital stay was longer among survivors with statistically significant difference (P-value = 0.01**)** as described in **table 5**

Table 5: Length of hospital stay and its association with mortality

	Outcome				t*		P value
	Alive		Deceased				
	Mean	SD	Mean	SD			
Length of Hospital Stay (days)	12.44	6.80	10.20	6.95	2.49		**0.01**

*Student t test - Bold is significant

Logistic regression analysis for risk factors of mortality showed that higher APACHE II score was an independent risk factor for mortality as described in **Table 6**.

Table 6: Logistic regression analysis for risk factors of mortality:

Risk factors of mortality	B	S.E.	P value	Odds ratio	95% C.I. for odds ratio	
					Lower	Upper
Age	.047	.054	.380	1.048	.944	1.164
Male gender	-.275	.765	.719	.760	.170	3.401
Presence of neurological symptoms on admission	.182	1.035	.860	1.200	.158	9.126
Presence of respiratory symptoms on admission	.896	1.102	.416	2.449	.283	21.225
BUN	.016	.016	.296	1.016	.986	1.048
D. Dimer	.066	.081	.417	1.068	.911	1.253
APACHE II score	.223	.088	**.011**	1.250	1.053	1.485
Constant	-7.117	3.886	.067	.001		

- Bold is significant

DISCUSSION

The study showed that 54% of the studied cases had neurocognitive manifestations on admission supporting the increasingly recognized importance of these manifestations in COVID-19, as supported by previous analysis showed that 78 of 214 (36.4%) patients in a study of patients with severe and non-severe conditions who are positive for COVID-19. [32]

Despite overlapping respiratory and neurocognitive symptoms of COVID-19 among participants, presence of neurocognitive symptoms on admission was significantly correlated with increased in-hospital mortality (P= 0.02). The study showed that the percentage of neurocognitive symptoms in deceased patients was significantly higher than among survivors. Also delirium and decline in conscious level were significantly more common in deceased patients. However there was no statistical significance between alive and deceased groups regarding other neurological manifestations including lateralization, aphasia and GTCs. These findings are supported by Mao et al., who found a statistically significant difference in neurological symptoms between the groups with severe and non-severe illness. Severe infections had a significantly greater prevalence of nervous system symptoms than non-severe infections (40 [45.5%] versus 38 [30.2%], P = 0.02). [6]

The study highlights the importance of delirium on hospital outcomes and supports the results of other studies where the presence of delirium was statistically significantly different between survivors and non-survivors [33]. Our results are consistent with Shao et al. systematic review and meta-analysis which found that the prevalence, incidence, and mortality rates for delirium in COVID-19 patients were 28.2%, 25.2%, and 48.4%, respectively, for patients older than 65. [34] In COVID-19 individuals, the prevalence, incidence, and mortality rates for delirium were respectively 15.7%, 71.4%, and 21.2% for patients under the age of 65. Overall, COVID-19 patients who experienced delirium had a greater risk of mortality than those who did not (Odd ratio: 3.2, 95% CI: 2.1–4.8). Also our results come in line with Pranata et al. systematic review and meta-analysis which reported that delirium was associated with higher risk of mortality. [35]

The study showed that the overall respiratory symptoms and fever were significantly more in the survivors group. Respiratory distress and hypoxia were significantly higher in deceased patients, while cough and fever were more in alive patients with statistically significant difference. Another study that supports our findings found that 88 out of 89 patients (98.9%) with oxygen saturation levels greater than 90% survived while 35 out of 51 patients (68.63%) with oxygen saturation values of 90% or less did not (log-rank P.001).[36] Additionally, Xie et al. reported a significant difference between the groups of survivors and non-survivors, with the non-survivors group experiencing higher levels of dyspnea. [37]

The study showed that no statistical significance was found between alive and deceased groups regarding age and gender. These results come in line with Poloni et al. who reported that there was no statistical significance between alive and deceased groups regarding age. [38] On the contrary, Mao et al. reported that there was statistical significance between severe disease group and non-severe disease group regarding age and sex. [6] This could be partially attributed to the fact that our study population exclusively included geriatric patients aged > 60 years.

Our current study showed that there was no statistical difference between the groups of survivors and non-survivors regarding comorbidities including DM, HTN, ISHD, AF, HF, CLD, CKD, CVS, chronic lung disease and malignancy. These data come in line with other studies which reported that there was no statistical significance between survivors and non survivors groups regarding various co morbidities. [6, 38, 39]

The study showed that TLC, serum sodium, BUN, serum creatinine, CRP, ferritin, D-dimer and APACHE II score were higher in deceased patients with statistically significant difference. While serum albumin was significantly lower in deceased patients. These results are supported with Mao et al. who reported that there was statistical significant difference between severe disease and non-severe disease groups regarding to serum BUN, creatinine, CRP, and D-Dimer. [6] Also these results are supported with Poloni et al. who reported that there was significant difference between alive and deceased groups regarding CRP being higher in deceased patients compared to survivors (P = 0·002). [38] Also our results are supported with another study reported that there was statistical significance between survivors and non-survivors regarding to serum CRP being higher in non-survivors compared to survivors group (114.2 [68.8–203.0] versus 57.2 [25·6–123], P = 0·001), and serum creatinine was greater in the group of the deceased compared to the group of the living. (0.99 [0.77–1.26] versus 0.87 [0.7–1.19)], P = 0·006). [39] Our results are consistent with another study reported a statistical significant difference between survivors and non-survivors regarding serum albumin, being lower in the deceased group compared to survivors group (37.6 ± 6.2 versus 30.5 ± 4.0, P < .001). [40]

The study showed that the mean length of hospital stay was more in alive patients with statistically significant difference. The shorter length of study among the dead group could be attributed to later presentation or more severe clinical condition on admission. Our results are supported with Wang et al. who demonstrated that the non-survivors' patients' hospital stays were significantly shorter. Only 5 days were spent in the hospital on average in the deceased group, compared to 28 days in the survivors group (5 (3–8) vs. 28 (26–29), P <0.001). [41]

In comparison to other potential risk factors of mortality in COVID-19 including age, male gender, presence of neurological or respiratory symptoms on admission, serum BUN, D-Dimer, the study showed that higher APACHE II score is an independent risk factor for mortality. Consistent with this finding, Xie et al. reported that APACHE II score was independently associated with increased risk of mortality. [37] In COVID-19 patients, Karthick et al. showed that APACHE II could be used as a predictor of hospital mortality, especially when the score is higher than 17. They highlighted the significance of APACHE II as a mortality early warning signal that could aid clinicians in implementing treatment strategies. [42]

Finally, our results couldn't be generalized due to the retrospective analysis and involvement of limited sample size at a single geriatric hospital. Also the overlapping symptoms on admission could have a confounding effect on the reported mortality. Further longitudinal studies are recommended.

Conclusion:

Neurocognitive manifestations were common among hospitalized geriatric patients with COVID-19 affecting about 54% of cases. Delirium and decline in conscious level were significantly associated with mortality. Higher APACHE II score was a predictor of mortality among these patients. Further longitudinal studies are recommended.

Conflict of interest: The Authors declared no conflict of interest

Contributions to the work: All authors contributed significantly to the work

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