Open Access

Original Article

Incidence of Determination of Magnitude of Confusion, Disorientation and Encephalopathy in Patients of COVID-19

Muhammad Waseem, Malik Nadeem Azam Khan, Asim Saleem, Majida Zia*, Saira Musarrat, Sana Uruj**

Department of Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan,
*Deparment of Medicine, Combined Military Hospital /National University of Medical Sciences (NUMS) Rawalpindi Pakistan,
**Department of Medicine, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the magnitude of confusion, disorientation, and encephalopathy in patients of COVID-19.
Study Design: Cross-sectional study.
Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi Pakistan, from May 2020 to Apr 2021.
Methodology: A total of 183 confirmed cases of COVID-19 who presented to our hospital and fulfilled the inclusion criteria were included. A confirmed COVID -19 case was diagnosed using real-time reverse transcriptase-polymerase chain reaction (rRT-PCR). Patient history and examination were done to document the neurologic symptoms. Coronavirus-related encephalopathy and COVID-19 severity were accessed using two distinct criteria. *p*-value of <0.05 was considered significant.
Results: The majority 110(60.1%) of the patients were between 46 to 70 years of age, and only 39.9% were between 20 to 45 years of age. There were a total of 23(12.6%) severe COVID-19 patients. Among them, 60.9% of severe COVID-19 patients were males Among severe COVID-19 patients, 52.2% had encephalopathy (*p*-value =0.002), a comparable percentage had confusion (*p*-value =0.002), and 39.1% has disorientation (*p*-value =0.032).
Conclusion: Neurological symptoms are more common among patients who had severe COVID-19, disease. Having additional knowledge about neurological symptoms would render physicians in limited resource settings, to focus on a mental health aspect that is usually ignored. This will make them more capable of dealing with COVID-19 patients, and thus providing treatment in a timely and efficient manner.

Keywords: Covid-19, Coronavirus, Confusion, Encephalopathy, Elevated, Neurological.

How to Cite This Article: *Waseem M, Khan MNA, Saleem A, Zia M, Musarrat S, Uruj S. Incidence of Determination of Magnitude of Confusion, Disorientation and Encephalopathy in Patients of COVID-19. Pak Armed Forces Med J 2025; 75(Suppl-2): S311-S315. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-2.7072*

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has led to over 26.5 million confirmed infections and there have been about 875,000 reported deaths from it globally.[1] COVID-19 manifest with flu-like symptoms and upper respiratory tract infections of varying severity.[2] COVID-19 can result in a multi-organ disease, with the involvement of the peripheral and central nervous systems in a few cases.[3]

Cytokine storm is triggered by hypoxia and results in acute respiratory distress syndrome and multiple organ failure. Encephalopathy is illustrated by dysfunction of the brain and is the result of metabolic changes and hypoxia.[4] COVID-19 patients who have hypoxia could have a fluctuating level of consciousness, which could vary from confusion to delirium, to coma. In neuroimaging, researchers have noted that sub-cortical and cortical T2/FLAIR signal deviations are the usual aberrations.[4] Neurotropism is a recognized feature of several coronaviruses. It appears to be the fundamental mechanism in several cases and is represented by an elevated proportion of anosmia among coronavirus cases.[5] The presence of ageusia and anosmia could aid in discerning from other types of encephalopathies.[6] There could be several causes of encephalopathy: metabolic, toxic, anoxic ischemic, inflammatory, and sepsis. Cases with encephalopathy may also furthermore have headaches, seizures, or extrapyramidal signs. Encephalopathy is a usual symptom of multiple organ dysfunction. This happens because the body fails to sustain normal brain function.[4] Consequently, we can deduce that neurological involvement can perhaps result in a complication of systemic disease. However, neurological manifestation could also be the main presentation. Physicians need to bear this in mind when assessing Covid-19 patients. In a study conducted in Pakistan, it was noted that 8.3% of COVID-19 patients had encephalopathy.[7] Studies have

Correspondence: Dr Muhammad Waseem, Department of Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan
Received: 12 Jul 2021; revision received: 05 Jan 2023; accepted: 06 Jan 2023

shown that there is evidence that a broad array of neurologic characteristics of COVID-19 infection have been documented, and researchers have noted that their severity is mounting.[8-10]

Physicians working in the emergency departments need to be cognizant of this fact so that when such patients present to the emergency department, they can recognize the neurological symptoms as a manifestation of COVID-19 infection.[5] Neurological symptoms are usually ignored specially in a country like Pakistan where mental health and its issues are considered at the bottom of the list. We planned this study to focus on and highlight the frequency of mental health issues like confusion, disorientation, and encephalopathy in COVID-19 cases.

METHODOLOGY

This cross-sectional study was conducted at Pak Emirates Military Hospital, Rawalpindi for a duration of six months (May 2020 to April 2021). Ethical approval was obtained from the institutional review board (IRB) vide reference number (A/28/EC/302/2021). After a thorough literature search, a sample size of 87 was calculated using a WHO calculator, keeping a 5% margin of error,95% confidence level, and a prevalence of neurological illness 6%.[11] Sampling was done using the nonprobability consecutive sampling technique. A maximum number of available participants (183) during the study period were recruited.

Inclusion Criteria: A confirmed COVID-19 case was defined based on the positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs.

Exclusion Criteria: Cases with AIDS, diabetes, chronic renal failure, electrolyte imbalance, hypertension, stroke, acute myocardial infarction, and those patients who were on immunosuppression therapy for any reason were excluded from our study as immunosuppressed patients tend to have discrete symptoms, which are rather diverse from the general population.

Before enrolling all patients, we obtained their written consent, and the confidentiality of the patients was ensured at all levels. If the patient was unable to provide consent, then we obtained it from their next of kin. The research questionnaires were kept under lock and key, in the principal investigators' office. We allocated a unique identifier to each case and removed all identifying information from the datasheet. Information about patient history, clinical examination findings, and tests were noted. A postgraduate, fellowship-trained neurologist reviewed and confirmed the findings.

The documentation of neurologic manifestations and COVID-19 symptoms onset dates were facilitated by patient history, physical examination, and neuroimaging.[3] Encephalopathy was recognized by the following criterion: (a) a doctor's diagnosis of encephalopathy, (b) any record of the occurrence of altered mental status or reduced level of consciousness, (c) a positive Confusion Assessment Method (CAM) assessment. The Confusion Assessment Method (CAM) validated and commonly used research and clinical tool for the documentation of delirium encephalopathy syndrome.[12]

COVID-19 related encephalopathy was recognized among the patients by the occurrence of any one or more than one of the following: (i) Changed level of consciousness with GCS of less than 13; (ii) Doctor acknowledged diagnosis of encephalopathy, by Confusion Assessment Method (CAM) of assessment; (iii) Computed tomography (CT) scan of the brain displaying: (a) Diffuse edema with effacement of the Cerebrospinal fluid (CSF)-containing spaces, or (b) Reduced cortical grey matter attenuation along with a loss of normal grey-white differentiation.

The severity of the COVID-19 patients having positive RT-PCR was labeled based on the presence of any one or more of the following: (i) respiratory rate ≥30/min on a clinical exam; (ii) oxygen saturation ≤93% on pulse oximeter; (iii) PaO2/FiO2 ≤300 mmHg on ABG; (iv) lung lesions progressed >50% within 24–48 hours on CT scan; (v) mechanical ventilation; (vi) shock: (vii) intensive care unit admission.[13]

Data were entered in Microsoft excel and later analyzed using Statistical Package for Social Sciences (SPSS) 21.0. Descriptive statistics were expressed as mean±standard deviation (SD). The Chi-square test was applied for qualitative data and an independent t-test was used for continuous variables. The *p*-value ≤0.05 was considered significant.

RESULTS

There were a total of 183 patients in our study. The majority 110(60.1%) of the patients were older, that is, between 46 to 70 years of age, whereas 39.9% were between 20 to 45 years of age. There were more male patients 109(59.6%), versus only 74(40.4%) female

patients. Disorientation was noted in 40(21.9%) patients; the confusion was noted in 47(25.7%) patients, and a comparable number of patients had encephalopathy 47(25.7%). There were 23(12.6%) severe COVID-19 patients in our study. 93(50.8%) had a duration of hospital stay of fewer than 72 hours, and 90(49.2%) patients had a duration of hospital stay of ≥72 hours Table-I.

Among those 47 patients who had confusion, 17(36.2%) were between 20 to 45 years of age, and 30(63.8%) were older, that is between 46 to 70 years old. More male patients 25(53.2%) were observed as having confusion as compared to female patients 22(46.8%). 27(57.4%) patients developed confusion within 72 hours of hospital admission, whereas 20(42.6%) patients developed confusion after 72 hours. Among those 47 patients who had encephalopathy, 17(36.2%) were younger, that is between 20 to 45 years of age. Whereas 30(63.8%) were older, that is, were between 46 to 70 years of age. When we looked at gender and encephalopathy, we found that more male patients 27(57.4%) had encephalopathy, as compared to 20(42.6%) female patients. 28(59.6%) patients who had encephalopathy, had a duration of hospital stay of fewer than 72 hours. A much smaller percentage of patients, that is 40.4%, had a duration of hospital stay greater than 72 hours Table-II.

Among severe COVID-19 patients. 52.2% had encephalopathy (p =0.002), a comparable percentage had confusion (p =0.002), and 39.1% has disorientation (p =0.032). There were 60.9% of severe COVID-19 patients were males and 60.1% were older patients, that is, between 46 to 70 years of age Table-III.

Table-I: Characteristics of patients with COVID-19

Variables	Categories	Number (%)
Age in years	20 to 45	73(39.9%)
	46 to 70	110(60.1%)
Gender	Males	109(59.6%)
	Females	74(40.4%)
Duration of hospital stay in hours	<72	93(50.8%)
	≥72	90(49.2%)
Disorientation	Yes	40(21.9%)
	No	143(78.1%)
Confusion	Yes	47(25.7%)
	No	136(74.3%)
Encephalopathy	Yes	47(25.7%)
	No	136(74.3%)
Severe COVID-19	Yes	23(12.6%)
	No	160(87.4%)

Table-II: Distribution of Characteristics of COVID-19 Patients According to the Neurological Symptoms

Variable	Categories	Response to Neurological Symptom Confusion		*p*-value
		Yes	No	
Age in years	20 to 45	17(9.3%)	56(30.6%)	0.54
	46 to 70	30(16.4%)	80(43.7%)	
Gender	Males	25(13.6%)	84(45.9%)	0.30
	Females	22(12.0%)	52(28.5%)	
Duration of hospital stay in hours	<72	27(14.7%)	66(36.2%)	0.29
	≥72	20(10.9%)	70(38.2%)	
Variable	**Categories**	**Response to Neurological Symptom Disorientation**		***p*-value**
		Yes	**No**	
Age in years	20 to 45	14(7.7%)	59(32.2%)	0.47
	46 to 70	26(14.2%)	84(45.9%)	
Gender	Males	23(12.5%)	86(47.1%)	0.76
	Females	17(9.3%)	57(31.1%)	
Duration of hospital stay in hours	<72	22(12.0%)	71(38.8%)	0.55
	≥72	18(9.8%)	72(39.4%)	
Variable	**Categories**	**Response to Neurological Symptom Encephalopathy**		***p*-value**
		Yes	**No**	
Age in years	20 to 45	17(9.3%)	56(30.6%)	0.54
	46 to 70	30(16.4%)	80(43.7%)	
Gender	Males	27(14.3%)	84(45.6%)	0.73
	Females	20(10.8%)	54(29.3%)	
Duration of hospital stay in hours	<72	28(15.3%)	65(35.5%)	0.16
	≥72	19(10.3%)	71(38.8%)	

Table-III: Characteristics of Covid-19 Patients According to Severity.

Variables	Categories	Severe COVID-19		*p*-value
		Yes n(%)	No n(%)	
Age in years	20 - 45	9(39.1%)	64(40%)	0.93
	46 - 70	14(60.9%)	96(60%)	
Gender	Males	14(60.9%)	95(59.4%)	0.89
	Females	9(39.1%)	65(40.6%)	
Disorientation	Yes	9(39.1%)	31(19.4%)	0.032
	No	14(60.9%)	129(80.6%)	
Confusion	Yes	12(52.2%)	35(21.9%)	0.002
	No	11(47.8%)	125(78.1%)	
Encephalopathy	Yes	12(52.2%)	35(21.9%)	0.002
	No	11(47.8%)	125(78.1%)	

**Statistically significant at a p-value of 0.05*

DISCUSSION

In our study 25.7% of the patients had encephalopathy. The majority of the patients (59.6%) were males, and 12.6% of the patients had severe COVID-19, disease. 63.8% of patients were older and 50.8% of patients had less than 72 hours of hospital admission when encephalopathy was noted. Chen *et*

al.,[14] assessed the clinical data of patients who had recovered (n=161) and those who had died (n=113) due to COVID-19 and noted that change in consciousness was more usual among those patients who died (22% versus 1%). This was comparable to our study, where neurological symptoms were more often seen among severe COVID-19 patients. The researchers also found that sepsis, acute respiratory distress syndrome (ARDS), acute myocardial injury, and electrolyte abnormalities, contributed to encephalopathy due to hypoxic and metabolic reasons.[14] In a study by Yin *et al*.,[15] it was shown that among 106 cases with neurological diseases there were 17 patients whose sensorium was altered. This was more frequently seen in critically and severely ill patients, and not so much among those with moderate to mild disease (13 out of 17 versus 4 out of 17 respectively).[15] These results are corroborated by the results from our study. Research conducted in China showed that among the 214 patients, there were 16(7.5%) patients who had suffered from impaired consciousness. Thirteen out of these sixteen patients were severe COVID-19 cases. The researchers found that patients who had a central nervous system (CNS) associated symptoms, also had thrombocytopenia, lymphopenia, and raised blood urea nitrogen levels. Chest abnormalities were usual among cases who had experienced CNS involvement.[16]

In the literature, it was found that when cases with severe and non-severe infection were compared, it was found that cases with severe infection were older. Even in our study 60.9% of the severe COVID-19 were older, that is, in the 46 to70 year range. In another study, it was noted that cases with severe infection had developed neurologic manifestations more often.[16] A high proportion of neurologic manifestations occurred early on in the disease period (the median time of hospital admission was about 1 to 2 days).[16] These results are comparable to our study, where neurologic manifestations occurred more in patients within 72 hours of hospital admission. Imao *et al*., found that few patients presented to the hospital with only neurologic symptoms as their presenting complaints. They had no typical symptoms such as cough, fever, diarrhea, or anorexia.[16] Hence, there is evidence to support the fact that as clinicians we need to pay close attention to patients' neurologic symptoms, chiefly those patients who are suffering from severe infection.[16] Furthermore, through the pandemic period of COVID-19, when observing patients with such neurologic symptoms, doctors must think of SARS-CoV-2 infection as a differential diagnosis. This should be done to avoid misdiagnosis or tardy diagnosis and hence avoid the prevention of disease transmission.[16]

In the literature, it was found that angiotensin-converting enzyme 2 (ACE 2) was recognized as the functional receptor for the coronavirus. This is present in several human organs, involving the nervous system.[17] The distribution and expression of ACE 2 remind us that the coronavirus might trigger some neurologic symptoms through indirect or direct mechanisms. There is evidence from the results of an autopsy conducted on COVID-19 patients that showed that the brain tissue was edematous and hyperemic and some of the neurons had degenerated.[16] Studies have documented that neurological injury has been established among patients of COVID-19 infection. Scientists have detected coronavirus nucleic acid was present in the cerebrospinal fluid of those cases and also was noted on autopsy in their brain tissue.[18-19]

Another research study validates that doctors should include in their differential diagnosis of delirium and confusion, the infection with the coronavirus, particularly among older adults.[20] The elderly population is of special concern irrespective of whether they have other symptoms of coronavirus infection or not.[20] This is imperative to prevent misdiagnoses of the patient and to better recognize severe cases of coronavirus infection to be at a higher risk for death and poor outcomes.[20] Additionally, research supports an urgent revision in Center for Disease Control (CDC) guidelines on the suggested profile of symptoms for coronavirus, and to include delirium as a significant coronavirus–related manifestation. Present CDC guidelines catalog newly found confusion among COVID-19 patients as an emergency warning sign.[20-22]

CONCLUSION

We noted that neurological symptoms were statistically significantly more common among patients who had severe COVID-19, disease. Overall, the frequency of these symptoms was higher among severe coronavirus patients. Particularly among those COVID-19 patients, who were older and had less than 72 hours of hospital admission. Developing countries do not have that many resources to invest in health care. This makes it important to find other COVID-19 symptoms that may play a role as a marker of coronavirus infection, at least among severe Covid-19 patients to save lives. Having additional knowledge about neurological symptoms would render physicians more

capable of diagnosing COVID-19 urgently, and thus providing treatment promptly.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MW & MNAK: Data acquisition, data analysis, critical review, approval of the final version to be published.

AS & MZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SM & SU: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. Ann Neurol 2020; 88(1): 1-1. https://doi.org/10.1002/ana.25807
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020 Jan 24. https://doi.org/10.1056/NEJMoa2001017
3. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020; 7(11): 2221-2230. https://doi.org/10.1002/acn3.51210
4. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. J Med Virol 2021; 93(1): 206-222. https://doi.org/10.1002/jmv.26207
5. Naidech AM, Beaumont JL, Rosenberg NF, Maas MB, Kosteva AR, Ault ML, et al. Intracerebral hemorrhage and delirium symptoms. Length of stay, function, and quality of life in a 114-patient cohort. Am J Respir Crit Care Med 2013; 188(11): 1331-1337. https://doi.org/10.1164/rccm.201307-1256OC
6. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. J Med Virol 2021; 93(1): 206-222. https://doi.org/10.1002/jmv.26207
7. Shafait S, Alamgir W, Yousaf MA, Manzar MA, Khattak AL, Yousaf MJ. Neurological Manifestations Of Covid-19 In Patients Admitted At A Tertiary Care Hospital In Punjab, Pakistan. PAFMJ 2020; 70(2): S439-S443.
8. Berger JR. COVID-19 and the nervous system. J Neurovirol 2020; 26(2): 143-148. https://doi.org/10.1007/s13365-020-00840-5
9. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020; 19(9): 767-783. https://doi.org/10.1016/S1474-4422(20)30221-0
10. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. J Neurol 2020; 267(6): 1573-1576. https://doi.org/10.1007/s00415-020-09896-z
11. Shafait S, Alamgir W, Yousaf MA, Manzar MA, Khattak AL, Yousaf MJ. Neurological Manifestations Of Covid-19 In Patients Admitted At A Tertiary Care Hospital In Punjab, Pakistan. PAFMJ. 2020; 70(2): S439-S443.
12. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Intern Med 1990; 113(12): 941-948. https://doi.org/10.7326/0003-4819-113-12-941
13. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018; 46(9): e825-73. https://doi.org/10.1097/CCM.0000000000003299
14. Chen T, Wu DI, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368. https://doi.org/10.1136/bmj.m1091
15. Yin R, Yang Z, Wei Y, Li Y, Chen H, Liu Z, et al. Clinical characteristics of 106 patients with neurological diseases and co-morbid coronavirus disease 2019: a retrospective study. medRxiv 2020 Jan 1. https://doi.org/10.1101/2020.04.29.20085415
16. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6): 683-690. https://doi.org/10.1001/jamaneurol.2020.1127
17. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GV, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203(2): 631-637. https://doi.org/10.1002/path.1570
18. Desforges M, Favreau DJ, Brison É, Desjardins J, Meessen-Pinard M, Jacomy H, et al. Human Coronaviruses Respiratory Pathogens Revisited as Infectious Neuroinvasive, Neurotropic, and Neurovirulent Agents. InNeuroviral infections 2013 (pp. 93-121). CRC press.
19. Al-Osail AM, Al-Wazzah MJ. The history and epidemiology of Middle East respiratory syndrome corona virus. Multidiscip Respir Med 2017; 12(1): 1-6. https://doi.org/10.1186/s40248-017-0101-8
20. Kennedy M, Helfand BK, Gou RY, Gartaganis SL, Webb M, Moccia JM, et al. Delirium in older patients with COVID-19 presenting to the emergency department. JAMA Netw Open 2020; 3(11): e2029540. https://doi.org/10.1001/jamanetworkopen.2020.29540
21. O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. Age Ageing 2020 Jul 1. https://doi.org/10.1093/ageing/afaa094
22. Burke RM, Killerby ME, Newton S, Ashworth CE, Berns AL, Brennan S, et al. Symptom profiles of a convenience sample of patients with COVID-19—United States, January–April 2020. MMWR Morb Mortal Wkly Rep 2020; 69(28): 904. https://doi.org/10.15585%2Fmmwr.mm6928a2