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In-Hospital predictors of severity and mortality among neuro-covid patients: a covid-19 retrospective case control study

Abstract

Background: Global studies have exemplified that COVID-19 has neurological manifestations. This study gives an insight to the impact of COVID-19 on the nervous system in Alexandria, Egypt and identifies in-hospital predictors of severity and mortality among Neuro-COVID patients.

Methods: This single centre, retrospective case-control study was conducted from August 1st, 2020 to January 31st, 2021, on patients admitted at the COVID-19 Isolation Hospital in Alexandria University, Egypt. A Neuro-COVID patient was defined as any patient with confirmed COVID-19 disease and evidence of one or more new onset nervous system clinical presentation.

Results: Out of 1073 in-patients, 352 were Neuro-COVID patients (183 [52%] females and 169 [48%] males). The mean age was 36.64 ± 18.97 years and 161 (45.7%) had comorbidities. Most common involvement was neuromusculoskeletal system (240 [68.2%]), followed by central nervous system (164 [46.6%]) and peripheral nervous system (125 [35.5%]), whereas, psychiatric disorders (4 [1.1%]) were the least common. Myalgia (215 [61.1%]); anosmia (118 [33.5%]); headache (100 [28.4%]); ageusia (80 [22.7%]); altered level of consciousness (56 [15.9%]); arthralgia (43 [12.2%]) and dizziness (12 [3.4%]) were predominant presentations. Female Neuro-COVID patients were twice as more likely to be critical than moderate (P =0.030). Critical cases with nervous system presentations manifested 12 times higher risk of death when compared to severe cases (P <0.001).

Conclusions: Nervous system involvement was predominant and clinically significant in COVID-19. Disease severity was identified as an independent predictor of mortality in hospitalised Neuro-COVID patients.

Keywords: SARS coronavirus, COVID-19, nervous system, neurological manifestation, Neuro-COVID, Alexandria, Egypt

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Osama S Abdelaziz, Zuraiha Waffa
Department of Neurosurgery, Faculty of Medicine, Alexandria University, Egypt

Correspondence: Osama S Abdelaziz, M.B.Ch.B., M.Ch., M.D, Professor of Neurosurgery, Department of Neurosurgery, Faculty of Medicine, Alexandria University, P.O. 21521, Alexandria, Egypt, Tel (+2) 01223153835; Fax (+203) 487-3076; Email Osama.Abdelaziz@alexmed.edu.eg

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Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; RT-PCR, real-time polymerase chain reaction; CNS, central nervous system; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; LOC, loss of consciousness; UMN, upper motor neuron

Introduction

The impact of Coronavirus Disease 2019 (COVID-19) on the nervous system is extensively researched during this dynamically evolving pandemic era.[1,2] Viral infections, such as human corona viruses (HCoV), are known to burden the nervous system and potentially lead to irreversible or fatal neurological conditions when the brain is compromised. This draws major concerns towards demanding resources and hospital workload experienced in the management of infectious disease outbreaks, particularly COVID-19.HCoV-229E, HCoV-OC43, severe acute respiratory syndrome coronavirus (SARS-CoV), HCoV-NL63, HCoV-HKU1, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were chronologically identified as HCoV strains. SARS-CoV and MERS-CoV were responsible for previous epidemics and global health concerns.[3] The nervous system has been established as a vulnerable tissue target to HCoVs.[4]

Various models of neuropathogenicity have attempted to explain why SARS-CoV-2, the highly pathogenic causative agent of COVID-19, has a profound affinity towards neural tissue. However, the exact underlying mechanisms of the olfactory route (neural circuit models) and the haematogenous route (cytokine storm theory), and how these translate to the neurological manifestations observed, are still under scrutiny.[5,6] Proposed theories on the neuropathology of SARS-CoV-2 include neurotropic and neuroinvasive mechanisms facilitated by angio-converting enzyme-2 (virus-induced neuropathology),[7,8] as well as misdirected autoimmune response leading to neuroinflammatory consequences (virus-induced neuro-immunopathology),[9] which overall promote neuronal cell injury.[6,10]

COVID-19 initially began as an outbreak in Wuhan, China in December 2019 and the World Health Organisation declared this a pandemic in March 2020, whilst, the first case in Egypt was reported in February 2020.[11,12] Clinical studies across the globe exemplify the involvement of nervous system in COVID-19[13–18] and neurological manifestations such as headache, dizziness, altered mental state, cerebrovascular events, smell/taste impairment, myalgia and psychosis are frequently associated with SARS-CoV-2 infection. Other researchers have analysed if risk factors including old age, underlying chronic illness and disease severity effect the neurological outcome of COVID-19 patients.[19–23]

Nevertheless, insufficient COVID-19 studies have represented the North African population.[24,25] This study emphasized the impact of COVID-19 in Alexandria, Egypt. The aim was to analyse the clinical findings and to identify the predictors of severity and mortality, among COVID-19 patients with nervous system clinical presentations. The clinical findings and content of this article were previously posted to the Research Square preprint server on May 13, 2022.

Methods

Study design

This single centre, retrospective case-control study was conducted from August 1st, 2020 to January 31st, 2021, on patients admitted at the COVID-19 Isolation Hospital in Alexandria University, Egypt. Patients admitted and managed at this hospital according to the guidelines of the World Health Organization (WHO) and the National Institute of Health (NIH). Patients were diagnosed with COVID-19 based on evidence for positive real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 using nasopharyngeal and throat samples. Neuro-COVID in-patients of both genders and all ages, categorized as moderate, severe or critical cases, were included in the study analysis. Non-Neuro-COVID patients and mild cases were excluded.

Definitions

A Neuro-COVID patient was defined as any patient with confirmed COVID-19 disease and evidence of one or more new onset nervous system clinical presentation. COVID-19 patients without any nervous system presentations and with only typical respiratory and/or other symptoms were described as Non-Neuro-COVID patients. Nervous system clinical presentations were further divided as signs and symptoms of central nervous system (CNS) involving the brain and/or spinal cord; peripheral nervous system (PNS) involving the cranial nerves and/or peripheral nerves; neuromusculoskeletal system (NMS) and psychiatric disorders (PSY). Gender was accounted as female or male and age was stratified into 5 age groups: <20 years; 20-39 years; 40-59 years; 60-79 years and ≥80 years. Comorbidities in patients were defined as a pre-existing chronic illness identified through past medical history and allocated as either neurological comorbidities or non-neurological comorbidities.

COVID-19 disease severity was categorized as moderate, severe and critical illness, according to the management of the patients admitted at the COVID-19 Isolation Hospital. Moderate cases were defined as patients who were monitored within the hospital wards, whereas severe cases required admission at the intensive care unit (ICU), and critical cases were indicated for intubation and mechanical ventilation. Mild cases were not admitted to this hospital and managed by home isolation. Clinical outcome was classified as either in-hospital deaths or discharges, which was identified as the end point for this study.

Data collection

Standardized data collection forms were used to obtain the patients data from medical records, including demographic data, medical history, clinical assessment and patient outcome. The required clinical findings were extracted and processed for analyses. Data ambiguities were resolved by discussion and reasoning between the authors.

Statistical analysis

Statistical functions were performed using IBM SPSS Statistics version 22.0. All the clinical findings in this study were categorical variables presented as counts (No.) and percentages (%). The distribution of clinical findings according to parameters including age, comorbidities, disease severity and mortality were compared using Chi-squared test or Fisher's exact test (Exact, *Monte Carlo*, or Asymptotic P *values* were chosen appropriately). Univariate and multivariate analyses employed to identify the predictors of COVID-19 disease severity and mortality in the studied patients, were expressed as Odds ratio (OR) and 95% confidence interval (95% CI). Selected variables with *P*-value <0.05 in the univariate analysis were included in multivariate analysis for adjusted models. The models used for disease severity and mortality were multinomial logistic regression and binomial logistic regression, respectively. Statistical significance was considered at *P*-value <0.05 for all analyses.

Results

Clinical findings of neuro-COVID patients hospitalized at the COVID-19 isolation hospital

This hospital treated 1073 COVID-19 patients during the study period. A total of 352 patients were included in the study analyses as these patients were diagnosed with COVID-19 who presented with clinical nervous system involvement (Neuro-COVID patients). As presented in Table 1, out of the total Neuro-COVID patients, 183 (52%) were females and 169 (48%) were males. The mean age was 36.64 ± 18.97 (range 17-95) years and thus, more patients were found in the younger age group 20-39 years (193 [54.8%]), followed by 60 (17%) patients aged 40-59 years; 55 (15.6%) patients aged 60 to 79 years; 37 (10.5%) patients aged <20 years and only 7(2%) patients were aged 80 years or above. Almost half of the total Neuro-COVID patients (161 [45.7%]) had underlying conditions including non-neurological (155 [44%]) and neurological comorbidities (24 [6.8%]). Most common nervous system involvement was NMS (240 [68.2%]), followed by CNS (164 [46.6%]) and PNS (125 [35.5%]), whereas, PSY presentations (4 [1.1%]) were the least common. Particularly, myalgia (215 [61.1%]); anosmia (118 [33.5%]); headache (100 [28.4%]); ageusia (80 [22.7%]); altered level of consciousness (LOC) (56 [15.9%]); arthralgia (43 [12.2%]) and dizziness (12 [3.4%]) were predominant in Neuro-COVID patients. Seizure, hypogeusia, paraparesis or paraplegia were each reported in 4 (1.1%) patients, whilst, other presentations reported in less than one percent of patients, included hemiparesis, aphasia, dysarthria, UMN facial palsy, unequal pupils, signs of meningitis, paraesthesia, faecal incontinence, urinary retention, hyposmia, blurred vision, visual hallucination, agitation, depressed mood, insomnia, suicidal thoughts and psychosis. Majority of Neuro-COVID patients were determined as moderate (271 [77%]) and there were 29 (8.2%) severe cases and 52 (14.8%) critical cases. Finally, the clinical outcome was 304 (86.4%) discharges and 48 (13.6%) deaths (Table 1).

Clinical findings according to age

Since Neuro-COVID patients were stratified into 5 age groups, patients below 40 years were determined as young and those 60 years or above as older patients, whilst those in between were middle aged. Table 1 shows that there were no significant differences between the age groups for females and males. More older patients had a history of comorbidities compared to the middle aged and younger patients (60-79 years= 92.7%; ≥80 = 85.7%; versus 40-59 years= 66.7%; 20-39 years= 29%; <20 years= 21.6%; *P* <0.001). Moreover, older Neuro-COVID patients presented with increased incidences of CNS manifestations (60-79 years= 74.5%; ≥80 years= 57.1%; versus 40-59 years= 51.7%; 20-39 years= 39.9%; <20 years= 29.7%; *P* <0.001) and either severe state (≥80 years= 28.6%; 60-79 years= 20%; versus 40-59 years= 13.3%; 20-39 years= 4.1%; <20 years= 0%; *P* <0.001), or critical state (≥80 years= 57.1%; 60-79 years= 50.9%; versus 40-59 years= 18.3%; 20-39 years= 4.7%; <20 years= 0%; *P* <0.001). This perhaps relates to higher incidences of deaths in older patients than other age groups (≥80 years= 71.4%; 60-79 years= 43.6%; versus 40-59 years= 18.3%; 20-39 years= 4.1%; <20 years= 0%; *P* <0.001). On the contrary, younger Neuro-COVID patients had more PNS manifestations (<20 years= 59.5%; 20-39 years= 44.6%; versus 40-59 years= 23.3%; 60-79 years= 5.5%; ≥80 years= 0%; *P* <0.001)

and NMS manifestations (<20 years= 81.1%; 20-39 years= 76.7%; versus 40-59 years= 65%; 60-79 years= 36.4%; ≥80 years= 42.9%; *P* <0.001), and since the majority were moderate cases (<20 years= 100%; 20-39 years= 91.2%; versus 40-59 years= 68.3%; 60-79 years= 29.1%; ≥80 years= 14.3%; *P* <0.001), they were more commonly discharged (<20 years= 100%; 20-39 years= 95.9%; versus 40-59 years= 81.7%; 60-79 years= 56.4%; ≥80 years= 28.6%; *P* <0.001) (Table 1).

Table 1 Distribution of clinical findings amongst Neuro-COVID patients with different ages

Variable	Age Group (years)						
	Total (n= 352)	**<20** (n= 37)	**20-39** (n= 193)	**40-59** (n= 60)	**60-79** (n= 55)	**≥80** (n= 7)	***P*-value**
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
Gender							
Female	183 (52.0)	18 (48.6)	107 (55.4)	28 (46.7)	26 (47.3)	4 (57.1)	0.675
Male	169 (48.0)	19 (51.4)	86 (44.6)	32 (53.3)	29 (52.7)	3 (42.9)	
Comorbidities[s]							
All	161 (45.7)	8 (21.6)	56 (29.0)	40 (66.7)	51 (92.7)	6 (85.7)	<0.001[1]
Neurological	24 (6.8)	1 (2.7)	6 (3.1)	4 (6.7)	12 (21.8)	1 (14.3)	<0.001[1]
Stroke	13 (3.7)	0	1 (0.5)	1 (1.7)	10 (18.2)	1 (14.3)	<0.001[1]
Brain/ spinal cord tumour	5 (1.4)	0	2 (1.0)	2 (3.6)	0	0	0.510
Epilepsy	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Alzheimer	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Hemiplegia	1 (0.3)	0	1 (0.5)	0	0	0	1.000
Cerebral palsy	1 (0.3)	0	0	1 (1.7)	0	0	0.450
Migraine	1 (0.3)	0	1 (0.5)	0	0	0	1.000
CVST	1 (0.3)	0	1 (0.5)	0	0	0	1.000
Myopathy	2 (0.6)	1 (2.7)	0	1 (1.7)	0	0	0.171
Psychiatric disorder	3 (0.9)	0	1 (0.5)	0	2 (3.6)	0	0.176
Non- Neurological	155 (44.0)	7 (18.9)	54 (28.0)	40 (66.7)	48 (87.3)	6 (85.7)	<0.001[1]
Hypertension	65 (18.5)	0	7 (3.6)	21 (35.0)	33 (60.0)	4 (57.1)	<0.001[1]
Diabetes	51 (14.5)	1 (2.7)	4 (2.1)	15 (25.0)	28 (50.9)	3 (42.9)	<0.001[1]
Asthma	25 (7.1)	5 (13.5)	12 (6.2)	6 (10.0)	2 (3.6)	0	0.286
Chronic sinusitis	12 (3.4)	0	12 (6.2)	0	0	0	0.045[1]
Renal disease	24 (6.8)	0	0	9 (15.0)	14 (25.5)	1 (14.3)	<0.001[1]
Cardiovascular disease	21 (6.0)	0	3 (1.6)	3 (5.0)	13 (23.6)	2 (28.6)	<0.001[1]
Malignancy	15 (4.3)	0	6 (3.1)	5 (8.3)	4 (7.3)	0	0.161
Benign tumour	2 (0.6)	0	1 (0.5)	0	1 (1.8)	0	0.519
Liver disease	11 (3.1)	0	2 (1.0)	3 (5.0)	4 (7.3)	2 (28.6)	0.001[1]
Blood disorder	9 (2.6)	0	3 (1.6)	6 (10.0)	0	0	0.015[1]
GIT disease	9 (2.6)	0	5 (2.6)	3 (5.0)	0	1 (14.3)	0.081
Rheumatic disease	9 (2.6)	1 (2.7)	2 (1.0)	4 (6.7)	2 (3.6)	0	0.177
Thyroid disease	3 (0.9)	0	1 (0.5)	2 (3.3)	0	0	0.223
PCOS	1 (0.3)	0	1 (0.5)	0	0	0	1.000
Smoking	9 (2.6)	0	3 (1.6)	1 (1.7)	2 (3.6)	3 (42.9)	<0.001[1]
Substance abuse	7 (2.0)	0	3 (1.6)	1 (1.7)	2 (3.6)	1 (14.3)	0.156
Clinical presentations [2]							
CNS	164 (46.6)	11 (29.7)	77 (39.9)	31 (51.7)	41 (74.5)	4 (57.1)	<0.001[1]
Headache	100 (28.4)	11 (29.7)	64 (33.2)	17 (28.3)	8 (14.5)	0	0.038*
Altered LOC	56 (15.9)	0	10 (5.2)	14 (23.3)	28 (5.09)	4 (57.1)	<0.001[1]
Dizziness	12 (3.4)	0	4 (2.1)	3 (5.0)	4 (7.3)	1 (14.3)	0.076
Seizure	4 (1.1)	0	0	2 (3.3)	1 (1.8)	1 (14.3)	0.014[1]
Paraparesis/ Paraplegia	4 (1.1)	0	1 (0.5)	2 (3.3)	1 (1.8)	0	0.318
Hemiparesis	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Aphasia	2 (0.6)	0	0	1 (1.7)	1 (1.8)	0	0.227
Dysarthria	2 (0.6)	0	0	2 (3.3)	0	0	0.102
UMN facial palsy	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Unequal pupils	1 (0.3)	0	0	1 (1.7)	0	0	0.450
Signs of meningitis	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Paraesthesia	3 (0.9)	0	2 (1.0)	1 (1.7)	0	0	1.000

Table Continued....

Variable	Age Group (years) Total (n= 352)	<20 (n= 37)	20-39 (n= 193)	40-59 (n= 60)	60-79 (n= 55)	≥80 (n= 7)	*P*-value
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Faecal incontinence	2 (0.6)	0	1 (0.5)	0	1 (1.8)	0	0.519
Urinary retention	1 (0.3)	0	1 (0.5)	0	0	0	1.000
PNS	125 (35.5)	22 (59.5)	86 (44.6)	14 (23.3)	3 (5.5)	0	<0.001[1]
Anosmia	118 (33.5)	22 (59.5)	81 (42.0)	13 (21.7)	2 (3.6)	0	<0.001[1]
Hyposmia	3 (0.9)	0	2 (1.0)	0	1 (1.8)	0	0.847
Ageusia	80 (22.7)	17 (45.9)	56 (29.0)	6 (10.0)	1 (1.8)	0	<0.001[1]
Hypogeusia	4 (1.1)	0	3 (1.6)	0	1 (1.8)	0	0.728
Blurred vision	2 (0.6)	0	1 (0.5)	1 (1.7)	0	0	0.704
NMS	240 (68.2)	30 (81.1)	148 (76.7)	39 (65.0)	20 (36.4)	3 (42.9)	<0.001[1]
Myalgia	215 (61.1)	27 (73.0)	133 (68.9)	34 (56.7)	18 (32.7)	3 (42.9)	<0.001[1]
Arthralgia	43 (12.2)	6 (16.2)	25 (13.0)	9 (15.0)	3 (5.5)	0	0.354
PSY	4 (1.1)	0	1 (0.5)	2 (3.3)	1 (1.8)	0	0.318
Visual Hallucination	2 (0.6)	0	0	1 (1.7)	1 (1.8)	0	0.227
Agitation	2 (0.6)	0	1 (0.5)	0	1 (1.8)	0	0.519
Depressed mood	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Insomnia	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Suicidal thoughts	1 (0.3)	0	0	0	1 (1.8)	0	0.279
Psychosis	1 (0.3)	0	0	1 (1.7)	0	0	0.450
Disease severity							
Moderate	271 (77.0)	37 (100.0)	176 (91.2)	41 (68.3)	16 (29.1)	1 (14.3)	<0.001[1]
Severe	29 (8.2)	0	8 (4.1)	8 (13.3)	11 (20.0)	2 (28.6)	<0.001[1]
Critical	52 (14.8)	0	9 (4.7)	11 (18.3)	28 (50.9)	4 (57.1)	<0.001[1]
Clinical outcome							
Deaths	48 (13.6)	0	8 (4.1)	11 (18.3)	24 (43.6)	5 (71.4)	<0.001[1]
Discharges	304 (86.4)	37 (100.0)	185 (95.9)	49 (81.7)	31 (56.4)	2 (28.6)	

CVST, cerebral venous sinus thrombosis; GIT, gastrointestinal tract; PCOS, polycystic ovary syndrome; CNS, central nervous system; LOC, loss of consciousness; UMN, upper motor neuron; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric

[1] *P*-value <0.05 was considered statistically significant.

[2] Patients were not mutually exclusive within this variable.

Clinical findings according to comorbidities

It is evident in Table 1 that, out of the total Neuro-COVID patients, the most common comorbidities were hypertension (65 [18.5%]), diabetes (51 [50.9%]), asthma (25 [7.1%]), renal disease (24 [6.8%]), cardiovascular disease (21 [6%]), stroke (18.2%), malignancy (15 [4.3%]) and liver disease (11 [3.1%]). **Table 2** shows that gender was not significantly distributed amongst Neuro-COVID patients with comorbidities. Age groups 40-59 years (with= 24.8% versus without= 10.5%; *P* <0.001) and 60-79 years (with= 31.7% versus without= 2.1%; *P* <0.001) had significantly more patients with comorbidities than without any comorbidities. Presence of comorbidities was more frequent in patients with CNS findings (with= 58.4% versus without= 36.6%; *P* <0.001), and less frequent in patients with PNS findings (with= 25.5% versus without= 44%; *P* <0.001) and NMS findings (with= 57.2% versus without= 77.5%; *P* <0.001). COVID-19 disease severity and outcome amongst the patients presenting with nervous system manifestations seem to be influenced by the presence comorbidities, as majority of cases with comorbidities warranted critical care attention (with= 28.0% versus without= 3.7%; *P*<0.001) and died in hospital (with= 26.7% versus without= 2.8%; *P*<0.001) (Table 2).

Table 2 Distribution of clinical findings amongst Neuro-COVID patients with comorbidities

Variable	Comorbidities with comorbidities (n = 161)	Without comorbidities (n = 191)	*P* -value
	No. (%)	No. (%)	
Gender			
Female	84 (52.2)	99 (51.8)	0.949
Male	77 (47.8)	92 (48.2)	
Age group (years)			
<20	8 (5.0)	29 (15.2)	0.002[1]
20-39	56 (34.8)	137 (71.7)	<0.001[1]

Table Continued....

Variable	Comorbidities with comorbidities (n = 161)	Without comorbidities (n = 191)	*P* -value
	No. (%)	**No. (%)**	
40-59	40 (24.8)	20 (10.5)	<0.001[1]
60-79	51 (31.7)	4 (2.1)	<0.001[1]
≥80	6 (3.7)	1 (0.5)	0.051
Clinical presentation [2]			
CNS	94 (58.4)	70 (36.6)	<0.001[1]
Headache	42 (26.1)	58 (30.4)	0.375
Altered level LOC	45 (28.0)	11 (5.8)	<0.001[1]
Dizziness	9 (5.6)	3 (1.6)	0.038[1]
Seizure	4 (2.5)	0	0.043[1]
Paraparesis/ Paraplegia	4 (2.5)	0	0.043[1]
Hemiparesis	1 (0.6)	0	0.457
Aphasia	2 (1.2)	0	0.208
Dysarthria	2 (1.2)	0	0.208
UMN facial palsy	1 (0.6)	0	0.457
Unequal pupils	0	1 (0.5)	1.000
Signs of meningitis	1 (0.6)	0	0.457
Paraesthesia	2 (1.2)	1 (0.5)	0.595
Faecal incontinence	2 (1.2)	0	0.208
Urinary retention	1 (0.6)	0	0.457
PNS	41 (25.5)	84 (44.0)	<0.001[1]
Anosmia	36 (22.4)	82 (42.9)	<0.001[1]
Hyposmia	1 (0.6)	2 (1.0)	1.000
Ageusia	22 (13.7)	58 (30.4)	<0.001[1]
Hypogeusia	1 (0.6)	3 (1.6)	0.628
Blurred vision	2 (1.2)	0	0.208
NMS	92 (57.2)	148 (77.5)	<0.001[1]
Myalgia	84 (52.2)	131 (68.6)	0.002[1]
Arthralgia	18 (11.2)	25 (13.1)	0.586
PSY	3 (1.9)	1 (0.5)	0.336
Visual Hallucination	2 (1.2)	0	0.208
Agitation	1 (0.6)	1 (0.5)	1.000
Depressed mood	1 (0.6)	0	0.457
Insomnia	1 (0.6)	0	0.457
Suicidal thoughts	1 (0.6)	0	0.457
Psychosis	1 (0.6)	0	0.457
Disease severity			
Moderate	92 (57.1)	179 (93.7)	<0.001[1]
Severe	24 (14.9)	5 (2.6)	<0.001[1]
Critical	45 (28.0)	7 (3.7)	<0.001[1]
Clinical outcome			
Deaths	43 (26.7)	5 (2.8)	<0.001[1]
Discharges	118 (73.3)	186 (97.4)	

CVST, cerebral venous sinus thrombosis; GIT, gastrointestinal tract; PCOS, polycystic ovary syndrome; CNS, central nervous system; LOC, loss of consciousness; UMN, upper motor neuron; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric

[1]*P*-value <0.05 was considered statistically significant.

[2]Patients were not mutually exclusive within this variable.

Clinical findings according to disease severity

As shown in Table 3, the distribution of Neuro-COVID females and males was not significant across the spectrum of moderate (M), severe (S) and critical (C) cases. Majority of moderate cases were found in the age group 20-39 years (M= 64.9% versus S= 27.6%; C= 17.3%; *P*<0.001). Severe and critical cases were highest in the age group 60-79 years (M= 5.9% versus S= 37.9%; C= 53.8%; *P*<0.001).Critical cases accounted for significantly higher reports of hypertension (44.2%), diabetes (36.5%), renal disease (26.9%), cardiovascular disease (15.4%), stroke (15.4%), liver disease (15.4%), malignancy (13.5%), substance abuse (9.6%) and brain tumours (3.8%), than other cases with comorbidities (M= 33.9%; S= 82.8% versus C= 86.5%;

P<0.001). CNS findings were more commonly exhibited in critical cases than severe and moderate (M= 38% versus S= 58.6%; C= 84.6%; *P*<0.001), yet vice versa for PNS findings (M= 43.9% versus S= 17.2%; C= 1.9%; *P*<0.001) and NMS findings (M= 76.8% versus S= 55.2%; C= 30.8%; *P*<0.001). Altered LOC was a serious CNS presentation since the highest frequency was observed within critical patients (73.1%), however, headache was most common amongst moderate patients (32.5%) instead of critical. Anosmia (42.1%), ageusia (28.8%), myalgia (68.6%) and arthralgia (14.8%) could be considered less serious presentations mainly exhibiting in moderate cases. Interestingly, albeit presenting at low frequencies, hyposmia (1.1%) and hypgeusia (1.5%) were only found within moderate cases; dysarthria (6.9%) and blurred vision (6.9%) were only found within severe cases; and faecal incontinence was only found within critical cases. All PSY findings ((M= 0%; S= 13.8%; C= 0%; *P*<0.001) were observed amongst severe cases. Seventy-eight percent of critical cases died as compared to 24% of severe cases, while 100% of moderate cases were discharged, and this distribution was statistically significant (*P*<0.001) (Table 3).

Predictors of severity

Table 3 demonstrates that age group 20-39 years, as well as, absence of stroke, hypertension, diabetes, renal disease, cardiac disease, malignancy and altered LOC were predictors revealed to be significantly associated with lower odds of severity in univariate logistic regressions comparing severe to moderate and critical to moderate cases, whereas, higher odds of severity were associated with absence of anosmia and myalgia in both univariate comparisons. Additionally, univariate logistic regression for critical compared to moderate cases identified female gender (OR 2.07; CI 1.11-3.88; *P*= 0.022) as a predictor with increased odds of severity. In the severe to moderate multivariate logistic regression, those aged 20-29 years were found to have a low risk of severity independently (adjusted OR 0.02; CI 0.002-0.28; *P*= 0.003) when model was adjusted for age group; neurological and non- neurological comorbidities; CNS, PNS and NMS presentations. When comparing critical to moderate cases, after adjustment for gender; age group; neurological and non- neurological comorbidities; CNS, PNS and NMS presentations, multivariate logistic regression confirmed that females, age group 20-39 years and absence of non-neurological comorbidities were significant independent predictors of severity in Neuro-COVID patients. Females were twice as more likely to be critical than moderate (adjusted OR 2.67; CI 1.10-6.48; *P*= 0.030). Patients aged 20 - 39 years ([absence] adjusted OR 0.04; CI 0.003-0.62; *P*= 0.021) and those without non-neurological comorbidities ([absence] adjusted OR 0.14; CI 0.05-0.41; *P* < 0.001) exhibited lower risks of being critical than moderate. Moreover, CNS presentation was not an independent predictor of severity, unlike patients admitted with PNS manifestations ([absence] adjusted OR 19.54; CI 2.30-166.09; *P*= 0.006) and NMS manifestations ([absence] adjusted OR 4.35; CI 1.47-12.87; *P*= 0.008) complaints with less likelihood, 1/20 and ¼, respectively, to present as critical cases than moderate (Table 3).

Clinical findings according to outcome

Figure 1 summaries the patient outcome indicating that the death rate was relatively higher in Neuro-COVID cases (13.6%) as compared to Non-Neuro-COVID cases (12.2%). Table 4 shows that out of 48 Neuro-COVID deaths, 28 (58.3%) females and 20 (41.7%) males died, although this was not statistically significant (*P*=0.344). Half of the patients who died were aged 60-79 years (deaths= 50% versus discharges= 10.2%; *P* <0.001) and majority of those discharged were 20-39 years (deaths= 16.7% versus discharges= 60.9%; *P* <0.001). Patients with underlying comorbidities faced more deaths than discharges (deaths= 89.6% versus discharges= 38.8%; *P* <0.001). Table 5 indicates that different parts of nervous system involved had a significant role on COVID outcome because more patients having CNS findings were found dead (deaths= 81.3% versus discharges= 41.1%; *P* <0.001), whereas, merely few incidences of death were amongst those with PNS involvement (deaths= 2.1% versus discharges= 40.8%; *P* <0.001) and NMS involvement (deaths= 33.3% versus discharge = 73.7%; *P* <0.001). Inevitably, death rates were predominant in patients determined severe (deaths= 14.2% versus discharges= 7.2%; *P* <0.001) and critical (deaths= 85.4% versus discharges= 3.6%; *P* <0.001) as seen in Table 6

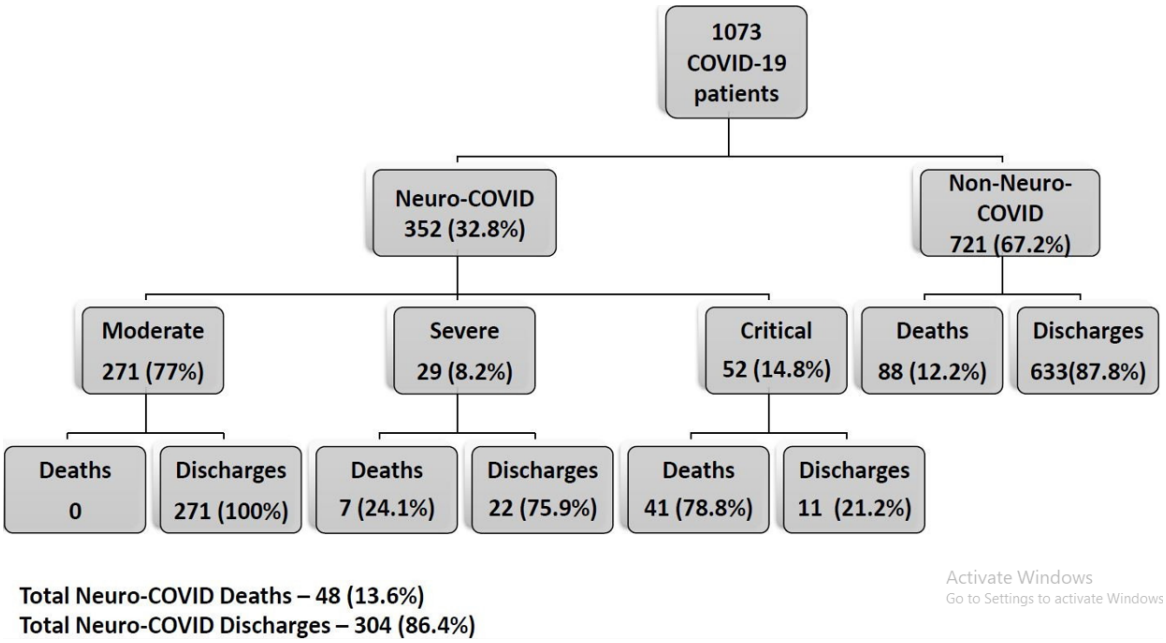

Figure 1 Flowchart showing the distribution of patients admitted to the COVID-19 Isolation Hospital.

Predictors of mortality

It is evident in Table 4–6 that univariate logistic regression demonstrates significant predictors of mortality in Neuro-COVID patients with increased the risk of death included, any comorbidities (OR 13.56; CI 5.22-35.21; *P* <0.001); neurological comorbidities (OR 5.45; CI 2.26-13.13; *P* <0.001) specifically stroke (OR 6.06; CI 1.94-18.90; *P*= 0.002); non-neurological comorbidities (OR 14.74; CI 5.67-38.31; *P* <0.001) including hypertension (OR 5.14; CI 2.67-9.87; *P* <0.001), diabetes (OR 4.93; CI 2.48-9.80; *P* <0.001), renal disease (OR 9.90; CI 4.12-23.76; *P* <0.001), cardiovascular disease (OR 5.62; CI 2.22-14.18; *P* <0.001), malignancy (OR 15.74; CI 5.11-48.49; *P* <0.001), liver disease (OR 12.81; CI 3.59-45.65; *P* <0.001), rheumatic disease (OR 5.44; CI 1.41-21.02; *P* =0.014), smoking (OR 8.72; CI 2.25-33.74; *P*= 0.002) and substance abuse (OR 17.56; CI 3.30-93.33; *P*= 0.001); CNS presentations (OR 6.21; CI 2.90-13.27; *P* <0.001) particularly altered LOC (OR 23.33; CI 11.24-48.45; *P* <0.001) and paraparesis/paraplegia (OR 20.20; CI 2.06-198.43; *P*= 0.010); and disease severity (OR 11.71; CI 3.98-34.49; *P* <0.001). Age group 20-39 years (OR 0.02; CI 0.003-0.10; *P* <0.001) and 40-59 years (OR 0.09; CI 0.02-0.53; *P*= 0.007); headache (OR 0.39; CI 0.17-0.90; *P*= 0.027); PNS findings (OR 0.03; CI 0.004-0.23; *P* <0.001) mainly anosmia (OR 0.03; CI 0.005-0.25; *P* <0.001), as well as NMS findings (OR 0.18; CI 0.09-0.34; *P* <0.001) mainly myalgia (OR 0.24; CI 0.12-0.46; *P* <0.001) were significant predictors found to decrease the risk of mortality. None of PSY findings were predictors of mortality. Multivariate logistic regression was adjusted for age group; neurological and non- neurological comorbidities; CNS, PNS and NMS presentations and disease severity. However, only disease severity emerged as the significant predictor of mortality in Neuro-COVID patients independent to other variables, emphasizing that critical cases with nervous system presentations manifested 12 times higher risk of death (adjusted OR 12.06; CI3.41-42.64; *P* <0.001) when compared to severe cases (Table 6)**.** Table 7 summarizes the statistically significant clinical findings amongst Neuro-COVID patients.

Table 4 Distribution of clinical findings for outcome and predictors of mortalities amongst Neuro-COVID patients - Demographics and Comorbidities.

Variable	Clinical Outcome			Deaths [1]			
	Deaths (n= 48)	Discharges (n= 304)	*P*-value	UVA[2]	*P*-value	MVA[3]	*P*-value
	No. (%)	No. (%)		OR (95% CI)		OR (95% CI)	
Gender							
Female	28 (58.3)	155 (51.0s)	0.344	1.35 (0.73-2.49)	0.345	-	
Male[4]	20 (41.7)	149 (49.0)		Ref		-	
Age group (years)							
<20	0	37 (12.2)	0.011[5]	-		-	
20-39	8 (16.7)	185 (60.9)	<0.001[5]	0.02 (0.003 - 0.10)	<0.001[5]	0.19 (0.009 - 3.72)	0.271
40-59	11 (22.9)	49 (16.1)	0.244	0.09 (0.02 - 0.53)	0.007[5]	0.24 (0.01 - 4.58)	0.339
60-79	24 (50.0)	31 (10.2)	<0.001[5]	0.31 (0.06 - 1.74)	0.183	0.13 (0.007 - 2.27)	0.161
≥80[4]	5 (10.4)	2 (0.7)	0.001[5]	Ref		Ref	
Comorbidities [6]							
All	43 (89.6)	118 (38.8)	<0.001[5]	13.56 (5.22 - 35.21)	<0.001[5]	-	
Neurological	10 (20.8)	14 (4.6)	<0.001[5]	5.45 (2.26 - 13.13)	<0.001[5]	0.71 (0.17 - 3.07)	0.650
Stroke	6 (12.5)	7 (2.3)	0.004[5]	6.06 (1.94 - 18.90)	0.002[5]	-	
Brain/ spinal cord tumour	2 (4.2)	3 (1.0)	0.139	4.36 (0.71 - 26.81)	0.112	-	
Epilepsy	1 (2.1)	0	0.136	-		-	
Alzheimer	1 (2.1)	0	0.136	-		-	
Hemiplegia	0	1 (0.3)	1.000	-		-	
Cerebral palsy	1 (2.1)	0	0.136	-		-	
Migraine	0	1 (0.3)	1.000	-		-	
CVST	0	1 (0.3)	1.000	-		-	
Myopathy	1 (2.1)	1 (0.3)	0.254	6.45 (0.40 - 104.83)	0.190	-	
Psychiatric disorder	1 (2.1)	2 (0.7)	0.357	3.21 (0.29 - 36.13)	0.345	-	
Non- Neurological	43 (89.6)	112 (38.8)	<0.001[5]	14.74 (5.67 - 38.31)	<0.001[5]	4.27 - (0.89 - 20.44)	0.069
Hypertension	22 (45.8)	43 (14.1)	<0.001[5]	5.14 (2.67 - 9.87)	<0.001[5]	-	
Diabetes	18 (37.5)	33 (10.9)	<0.001[5]	4.93 (2.48 - 9.80)	<0.001[5]	-	
Asthma	0	25 (8.2)	0.034[5]	-		-	
Chronic sinusitis	0	12 (3.9)	0.383	-		-	
Renal disease	13 (27.1)	11 (3.6)	<0.001[5]	9.90 (4.12 - 23.76)	<0.001[5]	-	
Cardiovascular disease	9 (18.8)	12 (3.9)	0.001[5]	5.62 (2.22 - 14.18)	<0.001[5]	-	
Malignancy	10 (20.8)	5 (1.6)	<0.001[5]	15.74 (5.11 - 48.49)	<0.001[5]	-	
Benign tumour	0	2 (0.7)	1.000	-		-	
Liver disease	7 (14.6)	4 (1.3)	<0.001[5]	12.81 (3.59 - 45.65)	<0.001[5]	-	
Blood disorders	3 (6.3)	6 (2.0)	0.110	3.31 (0.80 - 13.71)	0.099	-	
GIT disease	2 (4.2)	7 (2.3)	0.353	1.85 (0.37 - 9.15)	0.454	-	

Table Continued....

Variable	Clinical Outcome			Deaths [1]			
	Deaths (n= 48)	Discharges (n= 304)	*P*-value	UVA[2]	*P*-value	MVA[3]	*P*-value
	No. (%)	No. (%)		OR (95% CI)		OR (95% CI)	
Rheumatic disease	4 (8.3)	5 (1.6)	0.023[5]	5.44 (1.41 - 21.02)	0.014[5]	-	
Thyroid disease	0	3 (1.0)	1.000	-		-	
PCOS	0	1 (0.3)	1.000	-		-	
Smoking	5 (10.4)	4 (1.3)	0.003[5]	8.72 (2.25 - 33.74)	0.002[5]	-	
Substance abuse	5 (10.4)	2 (0.7)	0.001[5]	17.56 (3.30 - 93.33)	0.001[5]	-	

CVST, cerebral venous sinus thrombosis; GIT, gastrointestinal tract; PCOS, polycystic ovary syndrome; UVA, univariate analysis; MVA, multivariate analysis; OR, odds ratio; CI, confidence interval; Ref, reference.

[1]Comparing deaths to discharges

[2]Variables with frequency= 0 were not included in UVA.

[3]Selected variables with UVA *P*-value <0.05 were included in MVA; MVA adjusted for age group, neurological comorbidities, non-neurological comorbidities, CNS presentations, PNS presentations, NMS presentations, disease severity**;** using multinomial logistic regression model.

[4]Reference category for UVA and MVA within this group variable; all other variables were dichotomous (Presence versus Absence); Absence= reference category, Presence= tabulated OR (95% CI).

[5]*P*-value <0.05 was considered statistically significant.

[6]Patients were not mutually exclusive within this variable.

Table 5 Distribution of clinical findings for outcome and predictors of mortalities amongst Neuro-COVID patients - Clinical presentations

Variable	Clinical Outcome			Deaths [1]			
	Deaths (n = 48)	Discharges (n = 304)	*P*-value	UVA[2]	*P*-value	MVA[3]	*P*-value
	No. (%)	No. (%)		OR (95% CI)		OR (95% CI)	
Clinical presentations [4]							
CNS	39 (81.3)	125 (41.1)	<0.001[5]	6.21 (2.90 - 13.27)	<0.001[5]	0.70 (0.10 - 4.80)	0.717
Headache	7 (14.6)	93 (30.6)	0.022[5]	0.39 (0.17 - 0.90)	0.027[5]	-	
Altered level of consciousness	32 (66.7)	24 (7.9)	<0.001[5]	23.33 (11.24 - 48.45)	<0.001[5]	-	
Dizziness	3 (6.3)	9 (3.0)	0.216	2.19 (0.57 - 8.38)	0.254	-	
Seizure	2 (4.2)	2 (0.7)	0.091	6.57 (0.90 - 47.76)	0.063	-	
Paraparesis/ Paraplegia	3 (6.3)	1 (0.3)	0.009[5]	20.20 (2.06 - 198.43)	0.010[5]	-	
Hemiparesis	1 (2.1)	0	0.136	-		-	
Aphasia	2 (4.2)	0	0.018[5]	-		-	
Dysarthria	1 (2.1)	1 (0.3)	0.254	6.45 (0.40 - 104.83)	0.190	-	
UMN facial palsy	1 (2.1)	0	0.136	-		-	
Unequal pupils	1 (2.1)	0	0.136	-		-	
Signs of meningitis	0	1 (0.3)	1.000	-		-	
Paraesthesia	1 (2.1)	2 (0.7)	0.357	3.21 (0.27 - 36.13)	0.345	-	
Faecal incontinence	2 (4.2)	0	0.018[5]	-		-	
Urinary retention	1 (2.1)	0	0.136	-		-	
PNS	1 (2.1)	124 (40.8)	<0.001[5]	0.03 (0.004 - 0.23)	0.001[5]	0.25 (0.02 - 4.01)	0.330
Anosmia	1 (2.1)	117 (38.5)	<0.001[5]	0.03 (0.005 - 0.25)	0.001[5]	-	
Hyposmia	0	3 (1.0)	1.000	-		-	
Ageusia	0	80 (26.3)	<0.001[5]	-		-	
Hypogeusia	0	4 (1.3)	1.000	-		-	
Blurred vision	0	2 (0.7)	1.000	-		-	
NMS	16 (33.3)	224 (73.7)	<0.001[5]	0.18 (0.09 - 0.34)	<0.001[5]	0.65 (0.12 - 3.46)	0.613
Myalgia	15 (31.3)	200 (65.8)	<0.001[5]	0.24 (0.12 - 0.46)	<0.001[5]	-	
Arthralgia	2 (4.2)	41 (13.5)	0.067	0.28 (0.07 - 1.19)	0.085	-	
PSY	2 (4.2)	2 (0.7)	0.091	6.57 (0.90 - 47.76)	0.063	-	
Visual Hallucination	1 (2.1)	1 (0.3)	0.254	6.45 (0.40 - 104.83)	0.190	-	
Agitation	0	2 (0.7)	1.000	-		-	
Depressed mood	0	1 (0.3)	1.000	-		-	
Insomnia	0	1 (0.3)	1.000	-		-	

Table Continued....

Variable	Clinical Outcome			Deaths [1]			
	Deaths (n = 48)	Discharges (n = 304)	*P*-value	UVA[2]	*P*-value	MVA[3]	*P*-value
	No. (%)	No. (%)		OR (95% CI)		OR (95% CI)	
Suicidal thoughts	0	1 (0.3)	1.000	-		-	
Psychosis	1 (2.1)	0	0.136	-		-	

Abbreviations: CNS, central nervous system; LOC, loss of consciousness; UMN, upper motor neuron; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric; UVA, univariate analysis; MVA, multivariate analysis; OR, odds ratio; CI, confidence interval; Ref, reference.

[1]Comparing deaths to discharges.

[2]Variables with frequency= 0 were not included in UVA.

[3]Selected variables with UVA *P*-value <0.05 were included in MVA; MVA adjusted for age group, neurological comorbidities, non-neurological comorbidities, CNS presentations, PNS presentations, NMS presentations, disease severity**;** using multinomial logistic regression model.

[4]Patients were not mutually exclusive within this variable.

[5]*P*-value <0.05 was considered statistically significant.

Table 6 Distribution of clinical findings for outcome and predictors of mortalities amongst Neuro-COVID patients - Severity.

Variable	Clinical outcome			Deaths [1]			
	Deaths (n= 48)	Discharges (n= 304)	*P*-value	UVA[2]	*P*-value	MVA[3]	*P*-value
	No. (%)	No. (%)		OR (95% CI)		OR (95% CI)	
Disease severity							
Moderate	0	271 (89.1)	<0.001[5]	-		-	
Severe[4]	7 (14.6)	22 (7.2)	0.093	Ref		Ref	
Critical	41 (85.4)	11 (3.6)	<0.001[5]	11.71 (3.98 - 34.49)	<0.001[5]	12.06 (3.41 - 42.64)	<0.00[5]

UVA, univariate analysis; MVA, multivariate analysis; OR, odds ratio; CI, confidence interval; Ref, reference.

[1]Comparing deaths to discharges.

[2]Variables with frequency= 0 were not included in UVA.

[3]Selected variables with UVA *P*-value <0.05 were included in MVA; MVA adjusted for age group, neurological comorbidities, non-neurological comorbidities, CNS presentations, PNS presentations, NMS presentations, disease severity**;** using multinomial logistic regression model.

[4]Reference category for UVA and MVA within this group variable; all other variables were dichotomous (Presence versus Absence); Absence= reference category, Presence= tabulated OR (95% CI).

[5]*P*-value <0.05 was considered statistically significant.

Table 7 Summary of statistically significant clinical findings amongst Neuro-COVID patients

Variable	Clinical findings (n= 352)						
	Comorbidities		Disease severity			Clinical outcome	
	With (%)	Without (%)	Moderate (%)	Severe (%)	Critical (%)	Deaths (%)	Discharges (%)
Age Group (years)							
<20	5.0[1]	15.2[1]	13.7[1]	0	0	0	12.2[1]
20-39	34.8[1]	71.7[1]	64.9[1]	27.6[1]	17.3[1]	16.7[1]	60.9[1]
40-59	24.8[1]	10.5[1]	15.1[1]	27.6[1]	21.2[1]	22.9	16.1
60-79	31.7[1]	2.1[1]	5.9[1]	37.9[1]	53.8[1]	50.0[1]	10.2[1]
≥80	3.7	0.5	0.4[1]	6.9[1]	7.7[1]	10.4[1]	0.7[1]
Comorbidities[2]							
Neurological	-	-	2.6[1]	17.2[1]	23.1[1]	20.8[1]	4.6[1]
Non- Neurological	-	-	32.8[1]	72.4[1]	86.5[1]	89.6[1]	38.8[1]
Clinical presentations [2]							
CNS	58.4[1]	36.6[1]	38.0[1]	58.6[1]	84.6[1]	81.3[1]	41.1[1]
PNS	25.5[1]	44.0[1]	43.9[1]	17.2[1]	1.9[1]	2.1[1]	40.8[1]
NMS	57.2[1]	77.5[1]	76.8[1]	55.2[1]	30.8[1]	33.3[1]	73.7[1]
PSY	1.9	0.5	0	13.8[1]	0	4.2	0.7
Disease severity							
Moderate	57.1[1]	93.7[1]	-	-	-	0	89.1[1]
Severe	14.9[1]	2.6[1]	-	-	-	14.6	7.2

Table Continued....

Variable	Clinical findings (n= 352)						
	Comorbidities		Disease severity			Clinical outcome	
	With (%)	Without (%)	Moderate (%)	Severe (%)	Critical (%)	Deaths (%)	Discharges (%)
Critical	28.0[1]	3.7[1]	-	-	-	85.4[1]	3.6[1]
Clinical outcome							
Deaths	26.7[1]	2.8[1]	0	24.1[1]	78.8[1]	-	-
Discharges	73.3[1]	97.4[1]	100.0[1]	75.9[1]	21.2[1]	-	-

Variable (Predictor)	Predictors of Severity and Mortality					
	Severe [3]		Critical [4]		Deaths [5]	
	Univariate (OR)	Multivariate (OR)	Univariate (OR)	Multivariate (OR)	Univariate (OR)	Multivariate (OR)
Gender						
Female	0.82	-	2.07[1]	2.67[1]	1.35[1]	-
Male	Ref [6]	-	Ref [6]	-	Ref [7]	-
Age Group (years)						
<20	-	-	-	-	-	-
20-39	0.02[1]	0.04[1]	0.01[1]	0.04[1]	0.02[1]	0.19
40-59	0.10	0.10	0.07[1]	0.08	0.09[1]	0.24
60-79	0.34	0.22	0.44	0.26	0.31	0.13
≥80[6]	Ref [6]	Ref [6]	Ref [6]	Ref [6]	Ref [7]	Ref [7]
Comorbidities[2]						
Neurological	0.13[1]	0.27	0.09[1]	0.30	5.45[1]	0.71
Non- Neurological	0.17[1]	0.40	0.08[1]	0.14[1]	14.74[1]	4.27
Clinical presentations [2]						
CNS	0.043[1]	0.87	0.11[1]	0.47	6.21[1]	0.70
PNS	3.76[1]	2.19	39.93[1]	19.54[1]	0.03[1]	0.25
NMS	2.68[1]	1.90	7.43[1]	4.35[1]	0.18[1]	0.65
PSY	-	-	-	-	6.57	-
Disease severity						
Moderate	-	-	-	-	-	-
Severe	-	-	-	-	Ref [7]	Ref [7]
Critical	-	-	-	-	11.71	12.06

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric; OR, odds ratio; Ref, reference

[1]*P*-value was <0.05 and considered statistically significant.

[2]Patients were not mutually exclusive within this variable.

[3]Comparing severe cases to moderate cases; OR tabulated; refer to Table 3 for 95% confidence interval.

[4]Comparing critical cases to moderate cases; OR tabulated; refer to Table 3 for 95% confidence interval.

[5]Comparing deaths to discharges; OR tabulated; refer to Table 4 for 95% confidence interval.

[6]Reference category for univariate analysis and multivariate analysis within this group variable; all other variables were dichotomous (Presence versus Absence); Presence= reference category, Absence= tabulated OR.

[7]Reference category for univariate analysis and multivariate analysis within this group variable; all other variables were dichotomous (Presence versus Absence); Absence= reference category, Presence= tabulated OR.

Discussion

Two SARS-CoV-2 genome sequences were isolated in Egypt, contributing to the discovery of multiple strains of this evolving virus, which perhaps reflects upon how the course of the ongoing COVID-19 pandemic has been fluctuating.[26] Therefore interpreting the neuropathogenicity of SARS-CoV-2 was key to explaining how the direct and indirect interactions between SARS-CoV-2 and the nervous system at tissue level, manifested as neurological presentations in COVID-19 patients, varying across different study populations worldwide (Figure 2).[6,7,10]

The present study, conducted in Alexandria, Egypt during the second half of the pandemic in 2020, observed that the 32.8% (352/1073) of total patients admitted were Neuro-COVID patients. Raffino et al.[13] reported that 7.78% (137/1760) COVID-19 patients had neurological presentations in Bergamo, Italy, compared to 36.4% (78/214) in Wuhan, China as described by Mao et al.,[16] and although they were short duration studies, both took place during the initial wave of pandemic that engulfed these regions explaining the high influx of cases. Another Egyptian study conducted at Assiut and Aswan University Hospitals by Khedr et al.[25] reported that 50.6% (222/439) COVID-19 patients had neurological manifestations, whereas 45.1% (466/1034) Neuro- COVID patients were reported in a Tunisian study by Kacem et al.,[24] both showing higher rates of nervous system involvement than the present study cohort.

Mao et al.[16] reported CNS findings as most common (24.8%). The current study showed that the NMS (68.2%), were the most common part of nervous system involved in COVID-19 patients, followed by

CNS (46.6%) and PNS (35.5%). Regarding the PSY presentations, only few patients (1.1%) were observed in the present study, perhaps since psychiatric evaluation was not a routine assessment for all patients admitted with COVID-19, unless indicated by past medical history, in contrast to other reports of higher frequencies of psychosis (26%) in Varatharaj et al..[14] and anxiety (6.7%) in Khedr et al.[25]

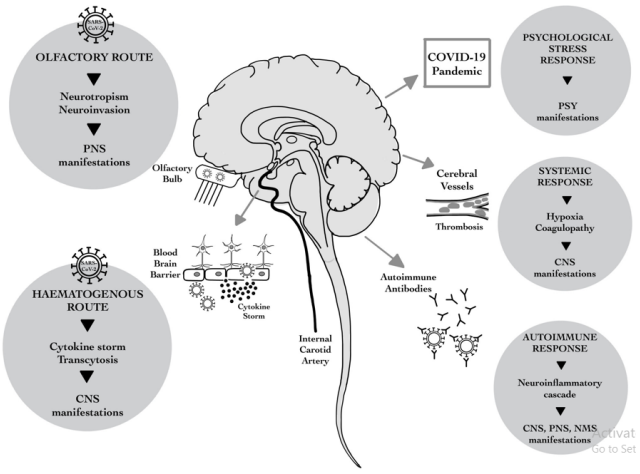

Figure 2 Schematic diagram illustrating the neuropathogenic pathways of SARS-CoV-2.

CNS, central nervous system; PNS, peripheral nervous system; NMS, neuromusculoskeletal; PSY, psychiatric

Most of the neurological clinical findings in the present study were consistent with previous studies including system reviews. Headache, dizziness, myalgia and arthralgia were considered non-specific neurological complaints, therefore, although these findings were predominant, they cannot be depended on when assessing COVID-19 prognosis.[25,27,28]

Fifty-six (15.9%) patients presented to the hospital with altered level of consciousness and were tested positive for SARS-CoV-2. This specific CNS manifestation was found to be associated with poor prognosis in the present study, as 73.1% were critical, highlighting that altered level of consciousness (LOC) should be considered a red flag finding in COVID-19. This is supported by Varatharaj et al.[14] who reported 39 (31%) cases with altered mental status. Moreover, Rifino et al.[13] diagnosed the cause of altered mental state in 49 (35.8%) patients using cerebrospinal fluid analysis and computer topography. The basic pathophysiology can be attributed to hypoxic state in Neuro-COVID patients with acute respiratory distress syndrome, depriving the brain from adequate oxygen levels.[18] Recent theory states that SARS-CoV 2 is capable of upregulating the neuro-inflammatory pathways and degrading the basement membrane to cross the blood brain barrier via transcytosis, which explains the altered LOC ranging from somnolence to complete loss of consciousness as reported within this study.[6]

The olfactory route of SARS-CoV-2 explains the high frequencies of anosmia (118.$^{33.5\%}$) and ageusia (80.$^{22.7\%}$) observed in the present study. The proximity of the olfactory neural circuit to respiratory droplets containing the virus, properties of viral neurotropism and direct interaction between virus particles and receptors on neural cells are factors identified as causes of direct injury of the olfactory nerve and impairment.[5] Garg et al.[17] found 24.5% anosmia and 33.1% ageusia in their case series. Similar results were reported by Kacemet al.[24] that had further analysed the rate of complete recovery from these chemosensory impairments (72.1% after anosmia and 76.8% after ageusia). Neuro-COVID patients with smell and taste impairments in the present cohort were mainly characterized as young and moderate cases, discharged without requiring intensive COVID-19 management, suggesting that PNS manifestations has better disease prognosis.

Although, stroke (18.2%) was identified, in the current study, as one of the pre-existing comorbidities before SARS-CoV-2 infection, other studies reported cerebrovascular events, as new onset manifestations of COVID-19.[14–16,18,25] Pre-existing neurological conditions are associated with higher risks of developing new onset neurological COVID-19 manifestations.[29]

The review by Abdelaziz and Waffa[10] advised that recognising significant risk factors was important to manage COVID-19 patients adequately. Multivariate analysis in the present study identified female Neuro-COVID patients as twice as more likely to be critical than moderate, which agrees with García-Azorínet al.[19] who confirmed that females, age and diabetes were significant risk factor for COVID-19 severity. Also, analysing the present cohort revealed disease severity as a new statistically significant risk factor for mortality. Critical cases with nervous system presentations manifested 12 times higher risk of death when compared to severe cases. Since most critically ill Neuro-COVID patients in this study presented with CNS manifestations (84.6%), it can be hypothesised that brain damage, brain herniation, invasive treatment, prolonged mechanical ventilation and exacerbated underlying comorbidities were the causes of death in these patients.[30]

Eskandar et al.[20] emphasised that old age and hypertension were risk factors for mortality, whereas, Salahuddin et al.[22] identified age as a predictor of mortality. These risk factors can be applied to assess immediate neurological prognosis of COVID-19; however, a greater sample size would provide profound results from multivariate analysis.

Certain strengths and weakness were highlighted during this present clinical research. Prolonged study period (6 months) and exposure to large population (1073 cases reviewed), enabled a profound analysis of the studied cohort. Therefore, it is one of the few North African studies to present substantial evidence for a wide range of nervous system findings in COVID-19 patients, and the first Alexandrian study to analyse potential predictors of COVID-19 severity and mortality. Limitations were mainly attributed to the study design. Since this was a single centre study, the findings were confined to a less diverse population. The retrospective design had limited access to follow-up patient data, required to identify long term neurological sequela of the disease and impact of the pandemic. A multi-centre prospective study should be considered to reflect a wider cohort and analyse the follow-up of discharged patients. Moreover, this study focuses on clinical findings and recommends extended analysis on laboratory and radiological data, as well as treatment protocols.

Conclusion

This in-patient cohort represents COVID-19 in Alexandria and confirms that nervous system involvement is predominant with SARS-CoV-2 infection and is clinically significant. The most involvement in patients hospitalized with COVID-19 exhibiting neurological manifestations (Neuro-COVID patients) was NMS, followed by CNS and then PNS, whereas PSY was the least common. Frequent neurological findings reported were myalgia/arthralgia, anosmia/ageusia, headache, and dizziness. Moreover, altered LOC was a serious CNS presentation since the highest frequency was observed within critical patients Strikingly, more patients were found in the younger age group 20-39 years than older age groups. Majority of cases with comorbidities were determined as critical cases. Inevitably, death

rates were predominant in patients determined severe and critical. On the other hand, all moderate cases were discharged. Female gender, young age group, absence of non-neurological comorbidities and PNS/NMS presentations were independent predictors of COVID-19 severity. Disease severity was identified as an independent predictor of mortality in Neuro-COVID patients. The CNS and PSY presentations did not significantly predict disease severity nor mortality. Overall, Neuro-COVID patients had higher death rates. Future regional multicentre research should elucidate the long-term neurological outcomes and complications of COVID-19 in Egypt.

Declarations

Ethics approval and consent to participate

This study was conducted with the approval of the review board of the Ethics Committee of the Faculty of Medicine, Alexandria University. Informed consents were obtained from all individual participants included in the study.

Consent for publication

Human research participants provided informed consent for publication of their data.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

Conceptualization: Osama S Abdelaziz and Zuraiha Waffa; Methodology: Osama S Abdelaziz and Zuraiha Waffa; Data collection and formal analysis: Zuraiha Waffa; Writing - original draft preparation: Zuraiha Waffa; Writing - review and editing: Osama S. Abdelaziz; Supervision: Osama S Abdelaziz. All authors read and approved the final manuscript.

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