Journal of Medicine in Scientific Research

Volume 5 | Issue 3 Article 12

Subject Area:

Neurological and musculoskeletal manifestations of coronavirus disease 2019: a retrospective study

Abeer H. Ismaiel
Mataria Teaching Hospital, abeerhussein2@yahoo.com

Wael M. El-Din Eldarandaly
Mataria Teaching Hospital

Recommended Citation

Ismaiel, Abeer H. and El-Din Eldarandaly, Wael M. (2022) "Neurological and musculoskeletal manifestations of coronavirus disease 2019: a retrospective study," *Journal of Medicine in Scientific Research*: Vol. 5: Iss. 3, Article 12.
DOI: https://doi.org/10.4103/jmisr.jmisr_51_22

Original Article

Neurological and musculoskeletal manifestations of coronavirus disease 2019: A retrospective study

Abeer H. Ismaiel[a], Wael M. El-Din Eldarandaly[b]

Departments of [a]Physical Medicine Rheumatology and Rehabilitation, [b]Critical Care, Mataria Teaching Hospital, Cairo, Egypt

Abstract

Objective

To study neurological and musculoskeletal (MSK) manifestations in coronavirus disease 2019 (COVID-19) patients with comorbidities compared with those without and study their association with COVID-19 disease severity.

Materials and methods

This is an observational, retrospective study. The data were collected from the first of January 2021 till the March 30, 2021, from electronic medical records in the ward and ICU of Mataria Teaching Hospital, and included 277 hospitalized COVID patients with examination and investigations confirming diagnosis of COVID-19 patients according to WHO interim guidance. The patients were presented with neurological and MSK manifestations. Neurological manifestations had presented in three sets: central nervous system manifestations (headache, dizziness, impaired consciousness, epilepsy, acute cerebrovascular disease, and seizure), peripheral nervous system manifestations (smell impairment, taste impairment, Guillain–Barre, and neuralgia), and MSK manifestations. We divided our patients into two groups, one with comorbidities and the other without, and compared both groups according to typical COVID-19 symptoms, neurological manifestations, laboratory findings, and severity of COVID-19 according to their respiratory status.

Results

We studied 277 patients whose mean (SD) age was 52.4 ± 14.5 years, 71 (53%) were females, and 63 (47%) were males with COVID-19 infection. Of all our patients, 134 (48.4%) had at least one of the underlying disorders. Those with high percentages were hypertension and diabetes. Of the patients, 122 (44%) had severe infection, and 155 (55.9%) patients had nonsevere infection according to their respiratory status. Of our patients 39.4% had nervous system manifestations. Comparing patients with nonsevere infection, patients with severe infection were older and had underlying diseases, especially hypertension and diabetes. They were manifested with fewer typical symptoms of COVID-19 and had more neurological manifestations, especially central nervous system manifestations in 39 (31.9%) patients versus 22 (14.2%), while peripheral nervous system manifestations were common in nonsevere patients. Thirty-four (21.9%) patients with nonsevere disease versus 14 (11.5%) patients with severe disease.

Conclusion

Neurological and MSK manifestations are commonly presented in patients with COVID-19 as an early manifestation and are not associated with the typical symptoms of COVID-19, and a few days later, the patients presented with severe respiratory manifestations associated with COVID infection, so clinicians should suspect this association to avoid the delayed diagnosis of the disease and for early isolation and effective treatment to decrease the incidence of case deterioration and decrease the mortality rate.

Keywords: Coronavirus disease 2019, neurological and musculoskeletal features, respiratory manifestations

Introduction

Coronavirus disease 2019 (COVID-19) is the disease associated with a novel coronavirus strain (SARS-CoV-2). The novel CoV showed similar symptoms to that of severe acute

Correspondence to: Dr. Abeer H. Ismaiel, MD, Department of Physical Medicine Rheumatology and Rehabilitation, Mataria Teaching Hospital, Cairo-11762, Egypt.
E-mail: Abeerhussein2@yahoo.com

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/jmisr.jmisr_51_22

Submitted: 11-May-2022 **Revised:** 27-May-2022 **Accepted:** 30-May-2022 **Published:** 23-Nov-2022

How to cite this article: Ismaiel AH, El-Din Eldarandaly WM. Neurological and musculoskeletal manifestations of coronavirus disease 2019: A retrospective study. J Med Sci Res 2022;5:270-9.

respiratory syndrome CoV (SARS-CoV) [1]. Both shared the same receptor, angiotensin-converting enzyme 2 (ACE2), and were diagnosed first in 2003 as CoV. Furthermore, thus, this virus was named SARS-CoV-2, and in February 2020, it was named COVID-19 by the WHO from Wuhan City in China, where a case was first reported in 2019 [2,3]. The disease is thought to be transmitted through droplets from human saliva, nose, and eyes. Humans who come in contact with such droplets through the same routes can get the virus into the body and the virus gets lodged in the lungs [2]. In the alveolar cells in the lungs, it will bind with the ACE2 and damage them leading to destruction. The alveolar cells have many essential roles in human respiration, and their damage can negatively alter the process of respiration. Thus, its impairment will alter the functions of those systems and organs, leading ultimately to a state of disequilibrium [3,4].

The mechanism of central nervous system (CNS) invasion is unclear, as coronaviruses do not primly target the nervous system, and their primary target is the respiratory epithelium. However, the authors suggested that the first mechanism is that the virus RNA is released in the cytoplasm, after its invasion of the respiratory cell and then translated and replicated after the formation of envelope proteins, then the virus pass to the circulation. ACE2 receptors are also present in the glial cells in the spinal neurons and the brain. Hence, the virus can bind to them. Coronavirus enters the brain and reaches the brain in about 7 days through a retrograde transfer via the olfactory epithelium or the cribriform bone [5].

During the viremia phase of illness, blood–brain barrier disruption causes the virus to enter the brain directly. Also, there is invasion of the virus through the peripheral nerve terminals and subsequently enter through the synapse to the CNS. Since COVID-19 has similarities with SARS-CoV, it can be concluded that, as discussed above, it also follows the same pathways for CNS invasion [6].

COVID-19 results in neurological damage primarily due to severe pneumonia, can result in systemic hypoxia leading to brain damage and secondary, immune-mediated injury by cytokine storms, and increased level of inflammatory mediators by the activation of T lymphocytes, macrophages, and endothelial cells [7].

Consequently, COVID-19 symptoms may be multiple and variable. Cough, fever, and headache are believed to be the most significant early symptoms of the disease [8].

However, in the nervous and musculoskeletal (MSK) systems, evidence is emerging of the effect of COVID-19 [9]. COVID-19's effects on the nervous and MSK systems may manifest as impaired olfactory function, anosmia, muscle weakness, myalgia, and Guillain–Barre syndrome [10]. However, not much evidence is found on these. The disease process is yet to be fully understood by scientists, including viral replication, pathogenicity, and epidemiology [11]. Some of these symptoms may precede the most familiar symptoms of COVID-19[12] in these patients. In addition, symptoms such as muscle weakness, myalgia, and headache may prove the patients' difficulties in carrying out daily living activities [13].

In addition, muscle weakness may result in muscle atrophy and contracture over time. Consequently, identifying the neurological and MSK features of the disease could prove beneficial and provide additional information that would aid in better understanding the diagnosis of COVID-19 and how to manage patients, as well as studying the relationship between disease severity and comorbidities such as hypertension, cardiac or cerebrovascular disease, diabetes mellitus, obesity, malignancy, chronic liver disease, and chronic kidney disease in patients with *C. avium* complex infection. This objective is crucial for raising awareness of the rapid clinical deterioration of patients with comorbidities in order to provide them with more care and early treatment.

Aim

This study aims to detect the neurological and MSK manifestations in COVID patients in the ward and ICU with and without comorbidities and to study their association with COVID-19 disease severity. This might be helpful in early diagnosis, prevention of disease spread, and aid in planning effective treatment.

Patients and methods

Study design and participants

The Ethics Committee approved the study protocol of GOTHI. This is an observational, retrospective case study. The data were collected from the first of January 2021 till the March 30, 2021 from electronic medical records in the ward and ICU of Mataria Teaching Hospital and included 277 hospitalized COVID patients with examination and investigations confirmed according to WHO interim guidance on the diagnosis of COVID-19 patients [14]. A positive result for COVID-19 was defined by real-time reverse-transcriptase-PCR assay analysis of throat swab specimens or high-throughput sequencing [3]. The protocol of the manufacturer (Shanghai bio-germ Medical Technology Co) using a SARS-CoV-2 nucleic acid detection kit. Chest radiographs and computed tomography (CT) were utilized for radiologic evaluations. According to the patient's clinical care needs, laboratory testing was performed, including a complete blood cell count, C-reactive protein, assessment of liver and renal function testing, creatine kinase and lactate dehydrogenase, blood chemical analysis, and coagulation testing. Arterial blood gases were also performed.

(1) Inclusion criteria: our study was retrospective, including all adult COVID-19 patients, with a mean age of 52.49 ± 14.91 years.
(2) Exclusion criteria: any patient who had an autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, vasculitis, or other autoimmune diseases, was excluded from the study.
(3) Data collection: we collected data from nursing records, electronic medical records, radiologic examinations, and

laboratory findings for all hospitalized COVID-19 patients in the ICU and the ward. We collected information on sex, age, comorbidities (hypertension, diabetes, cerebrovascular or cardiac disease, chronic kidney disease, and cancer), and symptoms from the onset to hospital admission (fever, anorexia, cough, throat diarrhea, and abdominal pain). In addition, neurological and MSK manifestations, laboratory results and CT scan (chest and head if available) were examined. Mentally and cognitively healthy conscious patients reported subjective symptoms. Patients' missing medical records were collected through direct communication with their families and health-care providers.

Using the American Thoracic Society's guidelines for community-acquired pneumonia, we determined the severity of COVID-19 (severe versus nonsevere) at the time of admission. 10 A validated definition includes at least one major criterion and at least three minor ones. Minor criteria: respiratory rate greater than 30 breaths per minute, PaO_2/FiO_2 ratio less than 250, and multilobar infiltrates confusion/disorientation, uremia (blood urea nitrogen concentration >20 mg/dl), leukopenia (white blood cell count, 4000 cells/ml), thrombocytopenia (platelet count, 100 000 cells/ml), hypothermia (core temperature, 368°C), and hypotension necessitating aggressive fluid resuscitation. Major factors: septic shock requiring the use of vasopressors [maintaining a mean arterial pressure of 65 mmHg and a serum lactate level of >2 mmol/l (18 mg/dl) despite adequate volume resuscitation] and failure of respiration necessitating mechanical ventilation.

The studied patients with neurological manifestations presented in three categories: central nervous system (CNS) manifestations (headache, dizziness, acute cerebrovascular disease, impaired consciousness, seizure, and ataxia), peripheral nervous system (PNS) manifestations (smell impairment, taste impairment, neuralgia, and Guillain–Barre), and MSK manifestations in the form of chest pain, myalgia, fatigue, arthralgia, and MSK injury manifestations.

Definition

Consciousness content (confusion and delirium) and the change of consciousness level (somnolence, stupor, and coma) are defined as impaired consciousness. Acute onset cerebrovascular disease includes cerebral hemorrhage and ischemic stroke, which head CT and clinical symptoms diagnose. Skeletal muscle injury in a patient with elevated serum creatine kinase level greater than 200 U/l (to convert to microkatals/liter, multiply by 0.0167) and skeletal muscle pain. Sepsis is defined as an organ dysfunction that is life threatening and caused by a response to infection by the host, which is unregulated. A subset of sepsis is the septic shock in which the underlying circulatory and cellular metabolism abnormalities increase mortality.

We classified our patients into two groups: group 1, patients with COVID-19 associated with comorbidities, and group 2 without comorbidities, and compared both groups according to the general symptoms of COVID-19, neurological and MSK manifestations and also by comparing both groups according to the laboratory and radiological manifestations. To study the association of disease severity with comorbidities and neurological and MSK manifestations, we subdivide our patients into two groups. Group 1 with severe disease and group 2 with nonsevere disease, we compare between them according to associated comorbidities, neurological, and MSK manifestations.

Ethical considerations

The study was approved by the institutional Ethics Committee of Matria Teaching Hospital NO. MTH-00012.

Statistical analysis

All tabulated data are expressed as mean ± SD for the normally distributed data. Comparisons between patients and control groups will be made using the Student's *t* test. As counts and percentages, the categorical variables were expressed. Using the Wilcoxon rank-sum test, continuous variables were compared, and the χ^2 test proportions for categorical variables were compared.

For all statistical tests, the significance will be done using the correlation coefficient (*r*) test, in which significance is defined as the level of *P* value of less than 0.05. Computations will be done using an SPSS statistical program, (version 21, Chicago, USA), and graphs will be assessed using Microsoft Excel. The significance threshold was set at a two-sided *P* value of less than 0.5.

Results

We analyzed 277 hospitalized COVID patients in the ward and ICU; examination and investigations confirmed the diagnosis of COVID-19 patients according to WHO interim guidance; 134 (48.4%) patients had comorbidities and 143 (51.6%) patients did not; their demographic and clinical characteristics are listed in Table 1. The mean (SD) age was 52 414.5 years, 71 (53%) were females, and 63 (47%) were males.

At the onset of illness, fever (227, 81.9%), cough (209, 75.5%), fatigue 160 (160, 57.8%), and anorexia (105,37.9%) were the most prevalent symptoms. As shown in Table 1, there were no statistically significant differences between the two groups regarding these symptoms.

One hundred and nine (39.4%%) patients of all COVID-19 patients had nervous system manifestations, 61 (22.2%) had CNS manifestations, and 48 (17.3%) had PNS manifestations.

Of the patients with comorbidities, 54.5% had nervous manifestations, compared with 25.2% of patients without comorbidities, a difference that was statistically significant ($P = 0.02$). Sixty-one (22.2%) patients had CNS, 42 (31.3%) patients had comorbidities, and 19 (13.3%) patients had CNS without comorbidities, with a significant difference of $P = 0.004$ between the two groups. There was no statistically

Table 1: Demographic and typical general clinical characteristics of patients with coronavirus disease 2019 associated with comorbidities compared with those with no comorbidities

Characteristics	Total (n=277)	With comorbidities (n=134) (48.4%)	Without comorbidities (n=143) (51.6%)	P
Age (mean±SD)	52.4±14.5	56.12±13.2	54.2±8.1	0.14
Age (year)				
<50	159 41.1±8.1	71 43.6±6.7	80 42.4±5.1	0.09
>50	118 66.7±5.8	63 67.2±5.4	63 66.6±5.2	0.28
Sex [n (%)]				
Female	147 (53.1)	71 (53)	76 (53.1)	0.9
Male	130 (46.9)	63 (47)	67 (46.9)	0.9
Typical symptoms [n (%)]				
Rhinorrhea	69 (24.9)	32 (24.6)	37 (25.8)	0.81
Fever	227 (81.9)	117 (87.3)	110 (76.9)	0.22
Fatigue	160 (57.8)	90 (67.2)	70 (48.9)	0.03
Cough	209 (75.5)	102 (76.1)	107 (74.8)	0.16
Anorexia	105 (37.9)	62 (47.3)	43 (30.1)	0.05
Diarrhea	16 (5.8)	8 (6)	8 (5.6)	0.096
Sore throat	79 (28.5)	35 (26.1)	44 (30.8)	0.6
Abdominal pain	40 (14.4)	18 (13.4)	22 (15.38)	0.82
Nausea, vomiting	48 (17.3)	17 (12.7)	31 (21.7)	0.04

significant difference between the two groups ($P > 0.05$) despite the fact that 48 (17.3%) patients exhibited PNS manifestations and 150 (54.2%) patients presented with MSK manifestations. Significant differences exist between 95 (70.9%) patients with comorbidities and 55 (38.5%) patients without comorbidities ($P = 0.01$). All CNS manifestations were significantly more prevalent in patients with comorbidities compared with those without comorbidities. In patients with PNS symptoms, the most frequently reported symptoms were taste impairment, olfactory impairment, and nerve pain as shown in Table 2. Patients with comorbidities reported these symptoms more frequently than those without them.

A more increased inflammatory response was found in patients with comorbidities, including neutrophil counts, higher white blood cell counts, elevated C-reactive protein levels, and lower lymphocyte counts compared with those without comorbidities. In addition, their D-dimer levels were higher than those of patients without the consumptive coagulation system. In addition, patients in the ICU with a severe infection had multiple organ involvement, including liver (increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels), kidney (increased blood urea nitrogen and creatinine levels), and skeletal muscle damage (increased creatinine kinase levels). In addition, ICU patients with underlying comorbidities exhibited severe respiratory symptoms, as demonstrated by a significant increase in the presence of fibrous strips and pleural thickening on CT scan as shown in Table 3.

The laboratory results of patients with and without CNS manifestations are shown in Table 4. We came to the conclusion that patients with CNS symptoms had lower platelet and lymphocyte counts. In addition to having lower lymphocyte and platelet counts, the group of patients with comorbidities associated with CNS symptoms also had lower lymphocyte levels. In the subgroup of patients without comorbidities, laboratory findings of patients with and without CNS manifestations did not differ significantly.

Table 5 provides the laboratory results of COVID-19 patients with and without PNS manifestations. We concluded that COVID-19 patients with PNS and those without PNS had no significant differences in laboratory manifestations. Similar findings were also detected in patients with comorbidities and without comorbidities groups when we compared laboratory manifestations in those with and without PNS.

Among all of our patients, 134 (48.4%) had at least one underlying disorder, with hypertension, diabetes, cerebrovascular disease, and ischemic heart disease having the highest prevalence. According to our study, 44% of ICU patients had a severe infection, while 55.9% had a less severe infection. Significantly more patients with severe infections had underlying disorders, particularly hypertension and ischemic heart disease. Also, as shown in Table 6, nervous symptoms were significantly more prevalent in patients with disease severity than in those without disease severity.

Patients in the ICU with severe diseases had significantly more central nervous manifestations than patients with less severe diseases. Forty-eight (17.3%) patients had PNS manifestations, which were significantly more prevalent in patients with mild disease than in those with severe disease. In all, 150 patients had MSK manifestations that were significantly more prevalent in ICU patients with severe disease than in those with less severe disease. All MSK manifestations, with the exception of arthralgia, were significantly higher in ICU patients with severe disease than in those with mild disease ($P = 0.01$).

The earliest neurological manifestations were acute cerebrovascular disease and impaired consciousness, which were typically unrelated to typical COVID-19

Table 2: Neurological and musculoskeletal clinical characteristics of patients with coronavirus disease 2019 associated with comorbidities compared with those with no comorbidities

Nervous system symptoms	Total (n=277) [n (%)]	With comorbidities (n=134) [n (%)]	Without comorbidities (n=143) [n (%)]	P
Any	109 (39.4)	73 (54.5)	36 (25.2)	0.03
CNS	61 (22.2)	42 (31.34)	19 (13.3)	0.004
Dizziness	45 (16.4)	35 (26.1)	10 (6.9)	0.00
Headache	46 (16.6)	29 (21.6)	17 (11.9)	0.03
Impaired consciousness	20 (7.1)	16 (11.9)	4 (2.8)	0.03
Cerebrovascular	14 (5.1)	10 (7.5)	4 (2.8)	0.04
Epilepsy	1 (0.4)	1 (0.4)	0	
Seizure	1 (0.4)	1 (0.4)	0	
PNS	48 (17.3)	31 (23.1)	17 (11.9)	0.14
Impaired taste	45 (16.6)	13 (9.7)	32 (22.3)	0.005
Impaired smell	41 (14.8)	12 (8.9)	29 (20.2)	0.008
Nerve pain	35 (5.2)	10 (7.5)	25 (19.5)	0.01
Guillain-Barre syndrome	7 (2.5)	2 (1.5)	5 (3.5)	0.3
MSK	150 (54.2)	95 (70.9)	55 (38.5)	0.01
Myalgia	138 (49.8)	76 (56.7)	62 (43.4)	0.03
Chest pain	145 (52.3)	92 (68.7)	53 (37.0)	0.00
Arthralgia	87 (31.4)	48 (35.9)	39 (27.3)	0.12
Skeletal muscle injury	31 (11.2)	27 (20.1)	4 (2.8)	0.00

CNS, central nervous system; MSK, musculoskeletal; PNS, peripheral nervous system.

Table 3: Laboratory and radiology findings in a patient with coronavirus disease 2019 associated with comorbidities compared with those without

Laboratory finding	Median (range) (n=277)	With comorbidities (n=134)	Without comorbidities (n=143)	P
Count (×10^9/l WBC)	4.8 (3.7-21.4)	6.5 (4.5-21.4)	5.2 (3.7-15.4)	0.005
Neutrophil	3.0 (0.1-17.5)	3.8 (0.1-12.1)	2.6 (0.7-17.5)	0.001
Lymphocyte	1.1 (0.1-2.8)	0.7 (0.1-2.6)	1.3 (0.5-2.8)	0.002
CK (U/l)	65 (8.9-12215)	84 (8.9-12215)	59 (0.2-1280)	0.003
LD (U/l)	252 (2.4-905)	310 (2.4-905)	210 (10.1-808)	0.004
Aminotransferase (U/l)				
Alanine	27 (5-1945)	32 (5-1945)	22 (6-161)	0.005
Aspartate	28 (9-821)	34 (9-821)	23 (8-144)	0.005
Blood urea nitrogen (mmol/l)	5.1 (1.6-49.2)	4.9 (1.6-49.2)	3.7 (1.6-13.8)	0.003
Creatinine (μmol/l)	65.2 (35.6-9425)	81.6 (35.6-9425)	66.5 (35.4-1293)	0.001
C-reactive protein (mg/l)	13.2 (0.5-215)	38 (0.5-215)	10.5 (0.6-125)	0.000
D-Dimer (mg/l)	0.3 (0.4-19.2)	0.9 (0.4-192)	0.4 (0.2-8.8)	0.04
Platelet	210 (17.3-590)	203.9 (18-466)	225 (53-591)	0.003
CT scan findings [n (%)]	220 (79.4)	110 (82.1)	110 (76.9)	0.28
Patchy shadows [n (%)]	163 (74.5)	86 (78.2)	77 (73.6)	0.48
Ground-glass opacity [n (%)]	91 (41.4)	52 (47.3)	39 (35.5)	0.07
Fibrous stripes [n (%)]	75 (34)	40 (36.4)	25 (22.7)	0.04
Pleural thickening [n (%)]	49 (22.3)	31 (28.1)	18 (16.4)	0.03

CK, creatine kinase; LD, lactate dehydrogenase; WBC, white blood ell.

symptoms (fever, cough, anorexia, and diarrhea). Twelve patients with acute cerebrovascular disease presented with hemiplegia and were admitted to the emergency department.

Their lung lesions were found to have a glass-like appearance on a lung CT scan, and they were diagnosed with COVID-19 based on a positive SARS-CoV-2 nucleic acid detection. However, in the later stages, they manifest all the typical symptoms of COVID-19. This patient may initially be diagnosed as a non-COVID patient and referred to the neurological ward. Later, the typical COVID symptoms, such as fatigue, sore throat, cough, decreased lymphocyte count, and the specific findings of acute inflammation of the lung tissue by chest CT scan in the form of a ground-glass appearance, manifest.

Discussion

Our retrospective case–control study was conducted on 277 hospitalized COVID patients in the ward and ICU at Mataria

Table 4: Laboratory findings of coronavirus disease 2019 patients with central nervous system in all patients and in patients with comorbidities and without

Laboratory finding	Median (range) Total with CNS symptoms ($n=109$)	no CNS	*P* value	Comorbidities with CNS symptoms ($n=109$)	no CNS	*P* value	Without comorbidities with CNS symptoms ($n=109$)	no CNS	*P* value
Count ($\times 10^9$/l) (WBC)	4.8 (0.4-13.4)	5.2 (3.7-21.4)	0.6	4.9 (0.4-12.5)	5.9 (3.5-16.4)	0.06	4.8 (2.5-11.4)	5.9 (5.4-21.8)	0.4
Neutrophil	2.8 (0.3-10.9)	3.5 (0.7-19.7)	0.4	3.8 (0.3-10.9)	4.4 (0.8-11.4)	0.2	2.2 (0.8-7.4)	2.9 (10.7-21.4)	0.1
Lymphocyte	1.0 (0.1-2.3)	1.6 (0.2-2.8)	0.05	0.6 (0.1-1.7)	0.9 (0.4-2.9)	0.01	1.3 (0.8-3.1)	1.5 (0.9-3.4)	0.05
Creatine kinase (U/l)	89 (7.8-12 219	60.5 (20-1270	0.2	109 (7.8-12 219)	64.5 (19-1260)	0.07	516 (30.1-1201)	49 (19-1106)	0.3
Lactate dehydrogenase, (U/l)	240 (2.4-87)	239 (3.3-908)	0.8	337 (2.5-890)	303 (2.9-743)	0.2	226 (122-808)	189 (2.9-420)	0.1
Aminotransferase, (U/l) alanine	27 (5-260)	24 (9-1838)	0.2	37 (7-1933)	31 (5-260)	0.3	25 (13-263)	22 (6-140)	0.7
Aspartate	28.5 (13-215)	30.2 (6-1190)	0.1	36.4 (14-211)	32 (8-601)	0.2	23.6 (13-180)	24.1 (13-170)	0.6
Blood urea	4.5 (1.6-49.2)	4.4 (1.5-19)	0.3	5.1 (2.3-47)	4.5 (1.6-20.1)	0.4	4.3 (1.5-39)	4.5 (1.6-20.1)	0.3
Creatinine (µmol/l)	70.4 (36.2-1198.1)	549 (35.9-1020)	0.06	72.8 (36.1-1199)	69.4 (35.9-9420)	0.3	71.8 (39.1-130.6)	62.2 (38.4-199)	0.2
C-reactive protein (mg/l)	14.1 (0.3-215)	10.2 (0.6-120)	0.31	42.4 (5.5-215)	29.2 (2.5-204)	0.6	7.9 (3.1-115)	9.2 (2.5-111)	0.7
D-dimer (mg/l)	0.5 (0.5-20.1)	0.5 (0.2-9.7)	0.8	0.9 (0.5-20)	1.2 (0.4-9.7)	0.3	0.4 (0.2-9.8)	0.2 (0.2-6.4)	0.5
Platelet	180 (19-567)	228 (45-570)	0.005	165 (17-330)	230 (90-560)	0.03	188 (20-550)	233 (56-580)	0.09

CNS, central nervous system.

Table 5: Laboratory findings of coronavirus disease 2019 patients with peripheral nervous system symptoms

Laboratory finding	Median (range) total with PNS symptoms ($n=109$)	no PNS	*P* value	Comorbidities with PNS symptoms ($n=109$)	no PNS	*P* value	Without comorbidities with PNS symptoms ($n=109$)	no PNS	*P* value
Count ($\times 10^9$/l) (WBC)	4.8 (2.7-8.5)	4.9 (0.2-20.4)	0.6	4.5 (3.8-6.9)	5.6 (0.3-20.4)	0.1	4.8 (1.8-8.5)	4.2 (1.9-16.8)	0.3
Neutrophil	2.8 (1.9-5.4)	3.5 (0.7-19.7)	0.7	2.9 (1.2-6.3)	4.3 (0.5-19.5)	0.2	2.8 (1.9-5.8)	2.6 (6.9-12.8)	0.7
Lymphocyte	1.8 (0.9-3.6)	1.5 (0.5-4.9)	0.4	1.9 (0.6-1.8)	0.9 (0.5-3.3)	0.3	1.4 (0.7-2.6)	1.3 (0.9-2.4)	0.8
Creatine kinase (U/l)									
Lactate dehydrogenase (U/l)	68 (32-1217)	68.5 (9.8-12218)	0.4	105 (32-1215)	83 (8.9-12218)	0.6	67 (44-177)	55.5 (19-1270)	0.3
Aminotransferase (U/l)	207 (2.6-517)	242 (2.6-908)	0.3	170 (4.5-5.19)	319 (2.9-808)	0.05	256 (5.5-471)	220 (3.9-809)	0.6
Alanine	27 (6-118)	29 (9-8231)	0.6	22 (8.2-85)	35.6 (12-1990)	0.3	23 (15-119)	24.5 (9.5-255)	0.5
Aspartate	22 (8-117)	27 (6-215)	0.3	22 (1.8-55)	35.9 (12-812)	0.1	24.6 (14-155)	23.5 (8-247)	0.9.7
Blood urea (mmol/l)	4.5 (1.8-9.7)	4.8 (1.5-98.1)	0.7	4.9 (3.9-12.8)	5.7 (1.6-50.2)	0.9	1.3 (1.9-7.3)	3.8 (1.7-14.7)	0.2
Creatinine (µmol/l)	62.8 (48.2-127.2)	68.9 (45.9-9435)	0.5	71.8 (59.3-129.4)	82.8 (35.8-9250)	0.8	59.5 (48.1-78.4)	66.9 (39.4-229.1)	
C-reactive protein (mg/l)	12.13. (1-74)	11.9 (0.1-212)	0.4	6.5 (3.2-81.2)	43.7 (0.6-212)	0.2	1.3 (3.2-91)	8.7 (0.5-126)	0.7
D-dimer (mg/l)	0.5 (0.3-8.5)	0.6 (0.2-9.7)	0.4	0.9 (0.4-21)	0.6 (0.3-9.9)	0.3	1.8 (0.4-20)	0.5 (0.4-4.9)	0.9
Platelet	204 (112-302)	209 (118-583)	0.5	195 (108-245)	215 (18-586)	0.6	204.5 (155-305)	219 (120-583)	0.7

PNS, peripheral nervous system.

Table 6: Comparison between patients with disease severity and those without as regards comorbidities, Neurological, and musculoskeletal manifestations

	Total *n*=277 [*n* (%)]	Severe [122 (44%)] [*n* (%)]	Nonsevere [155 (55.9%)] [*n* (%)]	*P*
Comorbidities				
Any	134 (48.4)	69 (56.6)	65 (41.9)	0.015
Hypertension	65 (23.4)	45 (36.9)	20 (12.9)	0.001
Diabetes	40 (14.4)	21 (17.2)	19 (12.3)	0.25
Cerebrovascular disease	21 (7.6)	12 (9.8)	8 (6.5)	0.31
Ischemic Heart disease	67 (24.2)	46 (37.7)	21 (13.5)	0.001
Chronic obstructive airway disease	11 (4.0)	7 (5.7)	4 (2.6)	0.2
Chronic liver disease	12 (4.3)	8 (6.7)	4 (2.6)	0.09
Malignancy	9 (3.2)	6 (4.9)	3 (1.9)	0.2
Chronic kidney disease	7 (2.5)	4 (3.3)	3 (1.9)	0.46
Nervous system symptoms				
Any	109 (39.4)	66 (54.1)	43 (27.7)	0.00
CNS	61 (22.2)	39 (31.9)	22 (14.2)	0.005
Dizziness	45 (16.4)	23 (18.9)	22 (14.2)	0.3
Headache	46 (16.6)	23 (18.9)	23 (14.8)	0.4
Impaired consciousness	20 (7.1)	18 (14.8)	2 (1.2)	0.00
Cerebrovascular	14 (5.1)	9 (7.4)	5 (3.22)	0.14
Epilepsy	1 (0.4)	1 (0.4)	0	
Seizure	1 (0.4)	1 (0.4)	0	
PNS	48 (17.3)	14 (11.5)	34 (21.9)	0.02
Impaired taste	45 (16.6)	13 (10.7)	32 (20.6)	0.03
Impaired smell	41 (14.8)	16 (10.3)	25 (20.5)	0.02
Nerve pain	35 (5.2)	23 (18.9)	12 (7.7)	0.05
Guillain-Barre syndrome	7 (2.5)	5 (4.1)	2 (1.3)	0.14
MSK	150 (54.2)	88 (72.1)	62 (40.0)	0.00
Myalgia	138 (49.8)	71 (58.2)	67 (43.2)	0.01
Chest pain	145 (52.3)	86 (70.5)	59 (38.1)	0.00
Arthralgia	87 (31.4)	41 (33.6)	46 (29.6)	0.5
Skeletal muscle injury	31 (11.2)	23 (18.9)	8 (5.1)	0.004

CNS, central nervous system; MSK, musculoskeletal; PNS, peripheral nervous system.

Teaching Hospital examination. Investigations confirmed the diagnosis of COVID-19 patients according to WHO interim guidance, with 134 (48.4%) patients with comorbidities and 143 (51.6%) patients without of all our patients, 134 (48.4%) had at least one of the underlying disorders; those with high percentages were hypertension in 65 (23.4%) patients, diabetes in 40 (14.4%) patients, cerebrovascular disease in 21 (7.6%) patients, and ischemic heart disease in 67 (24.2%) patients. We subdivide our patients into 122 (44%) patients in the ICU with severe infection and 155 (55.9%) patients in the ward with nonsevere infection. The patients with severe infection were significantly more likely to have underlying disorders, about 69 ((56.6%) patients versus 65 (41.9%) patients, especially hypertension, 45 (36.9%) patients versus 20 (12.9%) patients, and ischemic heart disease 46 (37.7%) patients versus 31 (20.0%) patients.

Similar results were noted in the first studied paper about detailed neurological manifestations of the hospitalized patients in the ward and ICU with COVID-b19. As of February 19, 2020, the authors studied 214 patients and classified them into two groups of patients; the first group had 88 (41.1%) patients who had a severe infection, and the second group had 126 (58.9%) patients with nonsevere infection. All neurological and MSK manifestations were present in 54.2%, including manifestations that involved CNS, PNS, and skeletal muscles [15].

In our study, there were 108 (39.4%) patients who had nervous system manifestations, 72 (53.7%) patients with comorbidities, especially hypertension and ischemic heart disease, and with few typical symptoms (fever, cough) versus 64 (25.8%) patients without comorbidities with significant difference, *P* value of 0.02. Also, nervous system symptoms were significantly manifested in patients with disease severity in the ICU compared with those in the ward without disease severity, and were about 66 (54.1%) patients in severe patients versus 43 (27.7%) patients in nonsevere patients.

Other authors confirmed our results, as they found that out of 214 studied patients with COVID, about 41.1% had a severe infection and 58.9% had a nonsevere infection. Seventy-eight (36%) COVID-19 patients had nervous system manifestations, and about 45.5% of them had severe disease and with underlying comorbidities, mainly hypertension, and ischemic heart disease, and had fewer symptoms of COVID-19 such as dry cough (34.1%) and fever (45.5%) [16].

Sixty-one (22.2%) of our COVID patients had CNS manifestations. The most common manifestations were dizziness present in 16.4% and headache present in 16.6%. Patients had CNS in 42 (31.34%) patients with comorbidities versus 19 (13.3%) patients without comorbidities. All CNS symptoms were higher in patients with comorbidities. Central nervous manifestations were significantly high in patients in the ICU with severe disease compared with patients with nonsevere disease present in 39 (31.9%) patients versus 22 (14.2%).

Forty-eight (17.3%) had PNS manifestations, with no significant difference between groups with and without comorbidities. They were significantly manifested in patients with nonsevere disease compared with those with severe disease and present in 14 (11.5%) patients with severe disease versus 34 (21.9%) patients with the nonsevere disease. They included loss of taste and smell in high percentage (16.6 and 14.8%), respectively, and were significantly manifested in patients with the nonsevere disease compared with patients with severe disease. Loss of taste was present in 10.7% and loss of smell was present in 10.3% in severe disease.

Recent research was consistent with our findings. They discovered that CNS manifestations were present in 24.8% of cases, while PNS manifestations were present in 8.9%. In patients with CNS manifestations, dizziness (16.8%) and headache (13.1%) were the most frequently reported symptoms, and they were significantly manifested in patients with severe infection. Taste impairment (5.6%) and olfactory impairment (5.1%) were the most frequently reported PNS symptoms in patients with mild infections [15].

The most common symptoms at the onset of illness were fever 227 (81.9%), cough 209 (75.5%), fatigue 160 (57.8%), and anorexia 105 (37.9%) in all the studied COVID patients; however, in patients with neurological manifestations, typical symptoms of COVID were present in few patients, and the first manifestations were central or peripheral mainly in severe cases.

The earliest neurological manifestations were acute cerebrovascular disease and impaired consciousness, usually not associated with typical symptoms of COVID-19 (fever, cough, anorexia, and diarrhea). Four patients presented with hemiplegia out of 12 patients with acute cerebrovascular disease and were admitted to the emergency department.

Their lung lesions were found by lung CT as glass-ground appearance and were diagnosed as having COVID-19 by a positive SARS-CoV-2 nucleic acid detection but appear in the later stage with all typical manifestations of COVID-19. In the first presentation, this patient may diagnose as a non-COVID patient and referred to the neurological ward. Later the typical COVID manifestation appears, such as fatigue, sore throat, cough, decreased lymphocyte count, and the specific findings of acute inflammation of the lung tissue by chest CT scan in the form of ground-glass appearance.

A previous study also reported that patients in the ICU with severe infection had underlying comorbidities as they present in older patients with hypertension and ischemic heart disease, but fewer typical symptoms such as fever and cough. Also, they develop neurological manifestations, especially disturbed consciousness, acute cerebrovascular disease, and MSK injury. Most nervous system manifestations occurred through 1–2 days without all typical symptoms (fever, diarrhea, cough, and anorexia) of COVID-19, and their presenting symptoms were only neurological manifestations [17].

Therefore, for patients with COVID-19, particularly those with severe infections, we must be vigilant and observant of any progression in their neurological manifestations and the emergence of any associated manifestations that may have contributed to their death. In addition, during the COVID-19 epidemic, physicians should consider SARS-CoV-2 infection as a differential diagnosis when evaluating patients with these neurological manifestations in order to avoid tiredness, prevent the spread of infection, and to determine the most effective treatment.

Recent studies have revealed that ACE2 is present in multiple human organs, including the nervous system and skeletal muscles, and has been identified as the functional receptor for SARS-CoV-2, which causes neurological manifestations through viral invasion. Other brain autopsy results of COVID-19 patients revealed brain tissue inflammation in the form of hyperemia, edema, and neuronal degeneration [12]. At autopsy, the SARS-CoV nucleic acid was found in the brain tissue and cerebrospinal fluid of these patients [18,19].

In our study, one of the main objectives was CNS manifestation caused by CNS invasion of SARS-CoV-2, leading to inflammation of the nervous system and the appearance of primary symptoms. SARS-CoV-2 may invade the CNS through the hematogenous route. However, peripheral nervous manifestations appear through its retrograde neuronal route. Our study found a decrease in lymphocyte cell count in patients with CNS manifestations and mainly in those with severe infections. These findings support that COVID-19 patients with CNS symptoms were more immunocompromised than patients without CNS manifestations. Moreover, we found that patients with disease severity had elevated D-dimer levels. This may be the reason for developing cerebrovascular disease in this subgroup [20].

Among the patients 15 (54.2%) had MSK manifestations and presented more in patients with comorbidities (70.9%). They were significantly manifested in patients in the ICU with severe disease compared with those with nonsevere disease and present in 88 (72.1%) patients with severe disease. Fatigue, chest pain, myalgia, and arthralgia were the most common MSK manifestations, represented at 57.8, 52.3, 49.8, and 31.4%, respectively.

Our results agreed with other studies where they found that there was a high prevalence of MSK manifestations in European studies. Authors studied 417 COVID-19 patients from 12 hospitals and found arthralgia in 31% and myalgia in 59% of these patients [21]. Different studies confirmed that fatigue was manifested in high prevalence presented in more than 50% of COVID-19 patients [22–24]. However, few studies suggested that myalgia and arthralgia had a higher prevalence [21,25,26].

One of the earliest manifestations in the early stage of the viral illness was MSK symptoms. They were presented in the form of fatigue, dry cough, fever, myalgia, and arthralgia, which are the common symptoms. In the late stages of the disease, MSK injury occurs, and patients necessitate intensive care. We found that patients with muscle symptoms, particularly those with severe infection, had higher creatine kinase and lactate dehydrogenase levels than those without muscle symptoms or severe infection.

The mechanism of MSK manifestations may be by indirect effects of viral infection, either arising from inflammatory or immune response or both together or by direct viral damage of the peripheral nerves or endothelium and causing muscle injury, which may be associated with ACE2 in the skeletal muscle [27].

From our findings, we have to advise planning a specific rehabilitation program in COVID-19 patients and detecting early-stage MSK symptoms associated with COVID-19 patients for early diagnosis and isolation of the patients to minimize the spread of disease and proper treatment stop the progression of the condition to late stage.

In conclusion, SARS-CoV-2 causes respiratory and extra respiratory manifestations by infecting either or both nervous and MSK systems on top of the respiratory tract. Neurologic involvement is high in severe infection and usually presented in COVID-19 patients with an underlying disease. In our study, we shed light on the importance of paying attention to the nervous symptom, which include dispersed consciousness, acute cerebrovascular diseases, and MSK injury, which appear as first manifestations without typical symptoms of viral infection, leading to the loss of cases, increase the spread of infection, and more deterioration of the condition. Also, late diagnoses of the associated infection causing difficulty of treatment in a timely manner and increasing the mortality rate. So, the clinician should be aware of the association between COVID-19 infection and neurological manifestations for proper early diagnosis and good treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Xu T, Chen C, Zhu Z, Cui M, Chen C, Dai H, *et al*. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. Int J Infect Dis 2020; 64:68–71.
2. Zhou P, Yang XL, Wang XG. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270–273.
3. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv 2020; 202:756–759.
4. Castranova V, Rabovsky J, Tucker JH, Miles PR. The alveolar type II epithelial cell: a multifunctional pneumocyte. Toxicol Appl Pharmacol 1988; 93:472–483.
5. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020; 11:995–998.
6. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 92:552–555.
7. Filalov A, Sharma P, Hindi F, *et al*. Neurological complications of corona virus disease (COVID-19): encephalopathy. Cureus 2020; 12:e7352.
8. Adhikari SP, Meng S, Wul Y-J, Mao Y-P, Ye R-X, Wang Q-Z, *et al*. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty 2020; 9:29.
9. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a review. Acta Neurol Scand 2020; 142:14–22.
10. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, *et al*. Guillain-Barre syndrome associated with SARS-CoV-2. N Eng J Med 2020; 382:2574–2576.
11. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020; 19:383–384.
12. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, *et al*. Neurological manifestations of COVID-19 (SARS-CoV-2): a review. Front Neurol 2020; 22:518.
13. Huang YH, Wu CY, Hsieh YW, Lin KC. Predictors of change in quality of life after distributed constraint-induced therapy in patients with chronic stroke. Neurorehabil Neural Repair 2010; 24:559–566.
14. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. January 2020. Available at: clinical-management-of-severe-acuterespiratory-infection-when-novel-coronavirus- (ncov)-infection-is-suspected. [Accessed February 5, 2020].
15. 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; 2020:1127.
16. Hai-Yang Wang , Xue-Lin Li , Zhong-Rui Yan, Xiao-Pei Sun, Han J and Bing-Wei Zhang. Beijing Hospital Confirms Nervous System Infections by Novel Coronavirus. China.org.cn 2020. Available at:. http://www.china.org.cn/china/2020-03/05/content_ 75777888.htm. [Last accessed on 2022 Apr 13].
17. Özdağ Acarlı AN, Samancı B, Ekizoğlu E, Çakar A, Şirin NG, Gündüz T, *et al*. Coronavirus disease 2019 (COVID-19) from the point of view of neurologists: observation of neurological findings and symptoms during the combat against a pandemic. Arch Neuropsychiatry 2020; 57:154–159.
18. Marc D, Dominique JF, Élodie B. Human coronavirus: respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neurovirulent agents. CRC Press 2013; 29:93–122.
19. Arabi YM, Balkhy HH, Hayden FG. Middle East respiratory syndrome. N Engl J Med 2017; 376:584–594.
20. Hartman-Maeir A, Soroker N, Ring H, Avni N, Katz N. Activities, participation and satisfaction one-year post stroke. Disabl Rehabil 2007; 29:559–566.
21. Escalera-Antezana JP, Lizon-Ferrufino NF, Maldonado-Alanoca A, *et al*. Clinical features of the first cases and a cluster of coronavirus disease 2019 (COVID-19) in Bolivia imported from Italy and Spain. Travel Med Infect Dis 2020; 35:101653.
22. Zheng Y, Xu H, Yang M. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. J Clin Virol 2020; 127:104366.

23. Parag G, Justin JC, Laura CP, Edward JS, Ruijun C, Assem J, *et al*. Clinical characteristics of Covid-19 in NewYork City. N Engl J Med Published Online First: 17 April 2020.
24. Lian J, Jin X, Hao S, *et al*. Analysis of epidemiological and clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. Clin Infect Dis 2020; 71:740–747.
25. Cabello-Verrugio C, Morales MG, Rivera JC, Cabrera D, Simon F. Renin-angiotensin system: an old player with novel functions in skeletal muscle. Med Res Rev 2015; 35:437–463.
26. Vetter P, Vu DL, L'Huillier AG, *et al*. Clinical features of covid-19. BMJ 2020; 369:1470.
27. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. Pediatrics 2020;145: e20200834. [Doi: https://doi.org/10.1542/peds.2020-0834].