

Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study

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ABSTRACT

OBJECTIVE

To study the neurological manifestations of patients with coronavirus disease 2019 (COVID-19).

DESIGN

Retrospective case series

SETTING

Three designated COVID-19 care hospitals of the Union Hospital of Huazhong University of Science and Technology in Wuhan, China.

PARTICIPANTS

Two hundred fourteen hospitalized patients with laboratory confirmed diagnosis of severe acute respiratory syndrome from coronavirus 2 (SARS-CoV-2) infection. Data were collected from 16 January 2020 to 19 February 2020.

MAIN OUTCOME MEASURES

Clinical data were extracted from electronic medical records and reviewed by a trained team of physicians. Neurological symptoms fall into three categories: central nervous system (CNS) symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms (hypogeusia, hyposmia, hypopsia, and neuralgia), and skeletal muscular symptoms. Data of all neurological symptoms were checked by two trained neurologists.

RESULTS

Of 214 patients studied, 88 (41.1%) were severe and 126 (58.9%) were non-severe patients. Compared with non-severe patients, severe patients were older (58.7 ± 15.0 years vs 48.9 ± 14.7 years), had more underlying disorders (42 [47.7%] vs 41

[32.5%]), especially hypertension (32 [36.4%] vs 19 [15.1%]), and showed less typical symptoms such as fever (40 [45.5%] vs 92 [73%]) and cough (30 [34.1%] vs 77 [61.1%]). Seventy-eight (36.4%) patients had neurologic manifestations. More severe patients were likely to have neurologic symptoms (40 [45.5%] vs 38 [30.2%]), such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]) and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]).

CONCLUSION

Compared with non-severe patients with COVID-19, severe patients commonly had neurologic symptoms manifested as acute cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms.

Introduction

In December 2019, many unexplained pneumonia cases occurred in Wuhan, China, and has rapidly spread to other parts of China, then to Europe, North America and Asia. This outbreak was confirmed to be caused by a novel coronavirus (2019 novel coronavirus, 2019-nCoV) [1]. 2019-nCoV was reported to have symptoms resembled that of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 [2]. Both shared the same receptor, angiotensin-converting enzyme 2 (ACE2) [3]. Therefore, this virus was named SARS-CoV-2, and recently WHO named it coronavirus disease 2019 (COVID-19). Until February 21th 2020, there were 75569 confirmed cases of COVID-19 and 2239 deaths in China [4].

Coronaviruses can cause multiple systemic infections or injuries in various animals [5]. However, some of them can adapt fast and cross the species barrier, such as in the cases of SARS-CoV and Middle East respiratory syndrome-CoV (MERS-CoV), causing epidemics or pandemics. Infection in human often leads to severe clinical symptoms and high mortality [6]. As for COVID-19, several studies have described clinical manifestations including respiratory symptoms, myalgia and fatigue. COVID-19 also has characteristic laboratory findings and lung CT abnormalities [7]. However, it has not been reported that patients with COVID-19 had any neurological manifestations. Here, we would like to report the characteristic neurological manifestation of SARS-CoV-2 infection in 78 of 214 patients with laboratory-confirmed diagnosis of COVID-19 and treated at our hospitals, which are located in the epicenter of Wuhan.

Methods

Study Design and Participants

This was a retrospective study. Data was reviewed on all patients with COVID-19 from January 16 to February 19, 2020 at three designated COVID-19 care hospitals of

Union Hospital of Huazhong University of Science and Technology. All patients with COVID-19 enrolled in this study were diagnosed according to the WHO interim guideline [8]. Only those cases confirmed by a positive result to real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay from throat swab specimens were included in the analysis [9]. Union Hospital, located in the endemic areas of COVID-19 in Wuhan, Hubei Province, is one of the major tertiary healthcare system and teaching hospitals responsible for the treatments for SARS-CoV-2 infection as designated by the government. The study was performed in accordance to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Verbal consent was obtained from patients before the enrollment.

Data Collection

The demographic characteristics, medical history, symptoms, clinical signs, laboratory findings, chest computed tomographic (CT) scan findings were extracted from electronic medical records. The data were reviewed by a trained team of physicians. Neurological symptoms were categorized into three main areas: central nervous system (CNS) symptoms or disease, peripheral nervous system (PNS) symptoms and muscular symptoms. Acute cerebrovascular disease included ischemic stroke and cerebral hemorrhage diagnosed by head CT. Muscle injury was defined when a patient had myalgia and elevated serum creatine kinase level above 200 U/L [7]. All neurological symptoms were reviewed and confirmed by two trained neurologists. The date of disease onset was defined as the day when the symptom was noticed. The severity of COVID-19 was defined by the international guidelines for community-acquired pneumonia [10].

Throat swab samples were collected and placed into a collection tube containing preservation solution for the virus [9]. SARS-CoV-2 was confirmed by real-time RT-PCR assay using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's protocol (Shanghai bio-germ Medical Technology Co Ltd).

Statistical Analysis

Continuous variables were described as means and standard deviations, or medians and interquartile range (IQR) values. Categorical variables were expressed as counts and percentages. Continuous variables were compared by using the unpaired Wilcoxon rank-sum test. Proportions for categorical variables were compared using the χ^2 test. All statistical analyses were performed using R (version 3.3.0) software. The significance threshold was set at a $P < 0.05$.

Results

Demographic and clinical characteristics

A total of 214 hospitalized patients with confirmed SARS-CoV-2 infection were included in the present analysis. Their demographic and clinical characteristics were shown in Table 1. Their average age was 52.7 ± 15.5 years, and 127 (59.3%) were females. Of these patients, 83 (38.8%) had at least one of the following underlying disorders: hypertension (51 [23.8%]), diabetes (30 [14.0%]), cardiovascular disease (15 [7.0%]), and malignancy (13 [6.1%]). The most common symptoms at onset of illness were fever (132 [61.7%]), dry cough (107 [50.0%]) and anorexia (68 [31.8%]). Seventy-eight (36.4%) patients had nervous system symptoms: CNS (53 [24.8%]), PNS (19 [8.9%]) and skeletal muscles (23 [10.7%]). In patients with CNS symptoms, the most common complaints were dizziness (36 [16.8%]) and headache (28 [13.1%]). In patients with PNS symptoms, the most common complaints were hypogeusia (12 [5.6%]) and hyposmia (11 [5.1%]).

According to the diagnostic criteria, 88 (41.1%) patients were severe and 126 (58.9%) patients were non-severe, respectively. The patients with severe infection were significantly older (58.2 ± 15.0 years vs 48.9 ± 14.7 years; $P < 0.001$) and more likely to have other underlying disorders (42 [47.7%] vs 41 [32.5%], $P < 0.05$), especially hypertension (32 [36.4%] vs 19 [15.1%], $P < 0.001$), and had less typical symptoms such as fever (40 [45.5%] vs 92 [73%], $P < 0.001$) and dry cough (30 [34.1%] vs 77 [61.1%], $P < 0.001$). Moreover, nervous system symptoms were significantly more common in severe cases as compared with non-severe cases (40 [45.5%] vs. 38 [30.2%], $P < 0.05$). They included acute cerebrovascular disease (5 [5.7%] (4 patients with ischemic stroke and 1 with cerebral hemorrhage who died later from respiratory failure) vs. 1 [0.8%] (1 patient with ischemic stroke), $P < 0.05$), impaired consciousness (13 [14.8%] vs. 3 [2.4%], $P < 0.001$) and muscle injury (17 [19.3%] vs. 6 [4.8%], $P < 0.001$).

Laboratory findings in severe patients and non-severe patients

Table 2 showed the laboratory findings in severe and non-severe subgroups. Severe patients had more increased inflammatory response, including higher white blood cell, neutrophil counts, lower lymphocyte counts and more increased C-reaction protein levels compared with those in non-severe patients (white blood cell: median, 5.4 [IQR, 0.1-20.4] vs 4.5 [IQR, 1.8-14.0], $P < 0.01$; neutrophil: median, 3.8 [IQR, 0.0-18.7] vs 2.6 [IQR, 0.7-11.8], $P < 0.001$; lymphocyte: median, 0.9 [IQR, 0.1-2.6] vs 1.3 [IQR, 0.4-2.6], $P < 0.001$; C-reaction protein: median, 37.1 [IQR, 0.1-212.0] vs 9.4 [IQR, 0.2-126.0], $P < 0.001$). The severe patients had higher D-dimer levels than non-severe patients (median, 0.9 [IQR, 0.1-20.0] vs 0.4 [IQR, 0.2-8.7], $P < 0.001$), which was indicative of consumptive coagulation system. In addition, severe patients had multiple organ involvement, such as serious liver (increased lactate dehydrogenase,

alanine aminotransferase and aspartate aminotransferase levels), kidney (increased blood urea nitrogen and creatinine levels) and muscle damage (increased creatinine kinase levels).

Laboratory findings in patients with and without CNS symptoms

Table 3 showed the laboratory findings of patients with and without CNS symptoms.

We found that patients with CNS symptoms had lower lymphocyte, platelet counts and higher blood urea nitrogen levels compared with those without CNS symptoms (lymphocyte: median, 1.0 [IQR, 0.1-2.3] vs 1.2 [IQR, 0.2-2.6], $P<0.05$; platelet: median, 180.0 [IQR, 18.0-564.0] vs 227.0 [IQR, 42.0-583.0], $P<0.01$; blood urea nitrogen: median, 4.5 [IQR, 1.6-48.1] vs 4.1 [IQR, 1.5-19.1], $P<0.05$). For the severe subgroup, patients with CNS symptoms also had lower lymphocyte, platelet counts and higher blood urea nitrogen levels compared with those without CNS symptoms (lymphocyte: median, 0.7 [IQR, 0.1-1.6] vs 0.9 [IQR, 0.2-2.6], $P<0.01$; platelet: median, 169.0 [IQR, 18.0-564.0] vs 220.0 [IQR, 109.0-576.0], $P<0.05$; blood urea nitrogen: median, 5.0 [IQR, 2.3-48.1] vs 4.4 [IQR, 1.5-19.1], $P<0.05$). For non-severe subgroup, there were no significant differences in laboratory findings of patients with and without CNS symptoms.

Laboratory findings in patients with and without PNS symptoms

Table 4 showed the laboratory findings of patients with and without PNS symptoms.

We found that there were no significant differences in laboratory findings of patients with PNS and those without PNS. Similar results were also found in the severe subgroup and non-severe subgroup, respectively.

Laboratory findings in patients with and without muscle injury

Table 5 showed the laboratory findings of patients with and without muscle injury.

Compared with the patients without muscle injury, patients with muscle injury had

higher neutrophil counts, lower lymphocyte counts and higher C-reactive protein levels, D-dimer levels (neutrophil: median, 4.3 [IQR, 0.9-18.7] vs 2.9 [IQR, 0.0-13.0], $P<0.05$; lymphocyte: median, 0.9 [IQR, 0.1-2.6] vs 1.2 [IQR, 0.1-2.6], $P<0.01$; C-reaction protein: median, 56.0 [IQR, 0.1-212.0] vs 11.1 [IQR, 0.1-204.5], $P<0.001$; D-dimer: median, 1.3 [IQR, 0.2-20.0] vs 0.5 [IQR, 0.1-20.0]). The abnormalities were manifestation of increased inflammatory response and blood coagulation function. In addition, we found that patients with muscle injury had multi-organ damage including more serious liver (increased lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels), and kidney (increased blood urea nitrogen and creatinine levels) abnormalities.

For the severe subgroup, patients with muscle injury had increased inflammatory response (decreased lymphocyte counts and increased C-reactive protein levels), and more serious liver (increased lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels), kidney (increased creatinine levels) and muscle damage (increased creatinine kinase levels). For non-severe subgroup, patients with muscle injury only had higher C-reactive protein and creatinine kinase levels compared with those without muscle injury.

Discussion

This is the first report on detailed neurologic manifestations of the hospitalized patients with COVID-19. As of February 19, 2020, of 214 patients included in this study, 88 (41.1%) were severe and 126 (58.9%) were non-severe. Of these, 78 (36.4%) had various neurologic manifestations involved CNS, PNS and skeletal muscles. Compared with non-severe patients, severe patients were older and had more hypertension but less with typical symptoms such as fever and cough. Severe patients were more likely to develop neurological symptoms, especially acute cerebrovascular

disease, conscious disturbance and muscle injury. Therefore, for patients with COVID-19, we need to pay close attention to their neurologic manifestations, especially for those with severe infections, which may have contributed to their demise. Moreover, during the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, doctors should consider SARS-CoV-2 infection as a differential diagnosis so to avoid delayed diagnosis or misdiagnosis and prevention of transmission.

Recently, ACE2 is identified as the functional receptor for SARS-CoV-2 [3], which is present in multiple human organs, including nervous system and skeletal muscle [11]. The expression and distribution of ACE2 remind us that the SARS-CoV-2 may cause some neurological symptoms through direct or indirect mechanisms.

Neurological injury has been confirmed in the infection of other coronavirus such as in SARS-CoV and MERS-CoV. The researchers detected SARS-CoV nucleic acid in the cerebrospinal fluid of those patients and also in their brain tissue on autopsy [12-13].

CNS symptoms were the main form of neurological injury in patients with COVID-19 in this study. The pathological mechanism may be from the CNS invasion of SARS-CoV-2, similar to SARS and MERS virus. Like other respiratory viruses, SARS-COV-2 may enter the CNS through the hematogenous or retrograde neuronal route. The latter can be supported by the fact that some patients in this study had hyposmia. We also found that the lymphocyte counts were lower for patients with CNS symptoms than without CNS symptoms. This phenomenon may be indicative of the immunosuppression in COVID-19 patients with CNS symptoms, especially in the severe subgroup. Moreover, we found severe patients had higher D-dimer levels than

that of non-severe patients. This may be the reason why severe patients are more likely to develop cerebrovascular disease.

Consistent with the previous studies [7] muscle symptom was also common in our study. We speculate that the symptom was due to skeletal muscle injury, as confirmed by elevated creatine kinase levels. We found that patients with muscle symptoms had higher creatine kinase and lactate dehydrogenase levels than those without muscle symptoms. Furthermore, creatine kinase and lactate dehydrogenase levels in severe patients were much higher than those of none-severe patients. This injury could be related to ACE2 in skeletal muscle [14]. However, SARS-CoV, using the same receptor, was not detected in skeletal muscle by post-mortem examination [15]. Therefore, whether SARS-CoV-2 infects skeletal muscle cells by binding with ACE2 requires to be further studied. One other reason was the infection-mediated harmful immune response that caused the nervous system abnormalities. Significantly elevated pro-inflammatory cytokines in serum may cause muscle damage.

This study has several limitations. First, only 214 patients were studied, which could cause biases in clinical observation. It would be better to include more patients from Wuhan, other cities in China, and even other countries. Second, all data were abstracted from the electronic medical records, certain patients with neurological problem might not be captured if their neurological symptoms were too mild, such as with hypogeusia and hyposmia. Third, because most patients were still hospitalized and information regarding clinical outcomes was unavailable at the time of analysis, it was difficult to assess the effect of these neurologic manifestations on their outcome, and continued observations of the natural history of disease are needed.

In conclusion, SARS-CoV-2 may infect nervous system, skeletal muscle as well as respiratory tract. In those with severe infection, neurological involvement is more

likely, which includes acute cerebrovascular diseases, conscious disturbance and skeletal muscle injury. Involvement of the nervous system carries a poor prognosis. Their clinical conditions may worsen and patients may die soon. Therefore, for patient with COVID19, physicians should pay close attention to any neurologic manifestations in addition to the symptoms of respiratory system.

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Table 1 Clinical characteristics of patients with COVID-19

	Total (n=214)	Severe (n=88)	Non-severe (n=126)	<i>P</i>
Age (y), means ± standard deviations	52.7±15.5	58.2±15.0	48.9±14.7	
Age, n (%)				<0.001
<50 y	90 (42.1)	24 (27.3)	66 (52.4)	
≥50 y	124 (57.9)	64 (72.7)	60 (47.6)	
Sex, n (%)				<0.05
Female	127 (59.3)	44 (50.0)	83 (65.9)	
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities, n (%)				
Any	83 (38.8)	42 (47.7)	41 (32.5)	<0.05
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<0.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	0.287
Cardio cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	0.651
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	0.841
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	0.694
Typical symptoms, n (%)				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<0.001
Dry cough	107 (50.0)	30 (34.1)	77 (61.1)	<0.001

Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	<0.05
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	0.1730
Pharyngalgia	31 (14.5)	10 (11.4)	21 (16.7)	0.278
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	0.214
Nervous system symptoms, n (%)				
Any	78 (36.4)	40 (45.5)	38 (30.2)	<0.05
CNS	53 (24.8)	27 (30.7)	26 (20.6)	0.094
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	0.415
Headache	28 (13.1)	15 (17.0)	13 (10.3)	0.151
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<0.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	<0.05
Ataxia	1 (0.5)	1 (1.1)	0 (0.0)	NA
Epilepsy	1 (0.5)	1 (1.1)	0 (0.0)	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	0.691
Hypogeusia	12 (5.6)	3 (3.4)	9 (7.1)	0.243
Hyposmia	11 (5.1)	3 (3.4)	8 (6.3)	0.338
Hypopsia	3 (1.4)	2 (2.3)	1 (0.8)	0.365
Neuralgia	5 (2.3)	4 (4.5)	1 (0.8)	0.074
Muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<0.001

Data are presented as means \pm standard deviations and n/N (%).

Abbreviations: CNS, central nervous symptoms; PNS, peripheral nerves symptoms.

P values indicate differences between severe and non-severe patients. $P < 0.05$ was considered statistically significant.

Table 2 Laboratory findings of patients with COVID-19

Median (range)	Total (n=214)	Severe (n=88)	Non-severe (n=126)	<i>P</i>
White blood cell count, ×10 ⁹ /L	4.9 (0.1-20.4)	5.4 (0.1-20.4)	4.5 (1.8-14.0)	<0.01
Neutrophil, ×10 ⁹ /L	3.0 (0.0-18.7)	3.8 (0.0-18.7)	2.6 (0.7-11.8)	<0.001
Lymphocyte count, ×10 ⁹ /L	1.1 (0.1-2.6)	0.9 (0.1-2.6)	1.3 (0.4-2.6)	<0.001
Platelet count, ×10 ⁹ /L	209.0 (18.0- 583.0)	204.5 (18.0- 576.0)	219.0 (42.0- 583.0)	0.251
C-reactive protein, mg/L	12.2 (0.1-212.0)	37.1 (0.1-212.0)	9.4 (0.4-126.0)	<0.001
D-dimer, mg/L	0.5 (0.1-20.0)	0.9 (0.1-20.0)	0.4 (0.2-8.7)	<0.001
Creatine kinase, U/L	64.0 (8.8- 12216.0)	83.0 (8.8- 12216.0)	59.0 (19.0- 1260.0)	<0.01
Lactate dehydrogenase, U/L	241.5 (2.2- 908.0)	302.0 (2.2- 880.0)	215.0 (2.5- 908.0)	<0.001
Alanine aminotransferase, U/L	26.0 (5.0- 1933.0)	32.5 (5.0- 1933.0)	23.0 (6.0- 261.0)	<0.05
Aspartate aminotransfer- ase, U/L	26.0 (8.0- 8191.0)	34.0 (8.0- 8191.0)	23.0 (9.0- 244.0)	<0.001
Blood urea nitrogen, mmol/L	4.1 (1.5-48.1)	4.6 (1.5-48.1)	3.8 (1.6-13.7)	<0.001

Creatinine, $\mu\text{mol/L}$	68.2 (35.9- 9435.0)	71.6 (35.9- 9435.0)	65.6 (39.4- 229.1)	<0.05
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P values indicate differences between severe and non-severe patients. $P < 0.05$ was considered statistically significant.

Table 3 Laboratory findings of COVID-19 patients with CNS symptoms

	Total			Severe			Non-severe		
	With CNS symptoms (n=53)	Without CNS symptoms (n=161)	<i>P</i>	With CNS symptoms (n=27)	Without CNS symptoms (n=61)	<i>P</i>	With CNS symptoms (n=26)	Without CNS symptoms (n=100)	<i>P</i>
Median (range)									
White blood cell count, ×10 ⁹ /L	4.6 (0.1-12.5)	4.9 (1.8-20.4)	0.582	5.3 (0.1-12.5)	5.5 (1.9-20.4)	0.769	4.1 (2.4-11.0)	4.6 (1.8-14.0)	0.397
Neutrophil, ×10 ⁹ /L	2.6 (0.0-10.9)	3.1 (0.7-18.7)	0.413	3.8 (0.0-10.9)	3.6 (0.7-18.7)	1.000	2.2 (0.9-7.4)	2.8 (0.7-11.8)	0.106
Lymphocyte count, ×10 ⁹ /L	1.0 (0.1-2.3)	1.2 (0.2-2.6)	<0.05	0.7 (0.1-1.6)	0.9 (0.2-2.6)	<0.01	1.3 (0.7-2.3)	1.3 (0.4-2.6)	0.492
Platelet count, ×10 ⁹ /L	180.0 (18.0-564.0)	227.0 (42.0-583.0)	<0.01	169.0 (18.0-564.0)	220.0 (109.0-576.0)	<0.05	188.5 (110.0-548.0)	232.0 (42.0-583.0)	0.093
C-reactive protein, mg/L	14.1 (0.1-212.0)	11.4 (0.1-204.5)	0.307	48.6 (0.1-212.0)	26.1 (0.1-204.5)	0.677	7.4 (3.1-111.0)	9.8 (0.4-126.0)	0.817
D-dimer, mg/L	0.5 (0.2-9.7)	0.5 (0.1-20.0)	0.750	1.2 (0.2-9.7)	0.9 (0.1-20.0)	0.424	0.4 (0.2-6.4)	0.4 (0.2-8.7)	0.455
Creatine kinase, U/L	79.0 (8.8-12216.0)	60.5 (19.0-1260.0)	0.167	104.0 (8.8-12216.0)	64.0 (19.0-1214.0)	0.081	52.5 (28.0-206.0)	59.0 (19.0-1260.0)	0.561
Lactate dehydrogenase, U/L	243.0 (2.2-880.0)	241.0 (3.5-908.0)	0.766	334.0 (2.2-880.0)	299.0 (3.5-743.0)	0.324	198.0 (2.5-417.0)	226.0 (121.0-908.0)	0.142

Alanine aminotransferase, U/L	27.0 (5.0-261.0)	26.0 (6.0-1933.0)	0.214	35.0 (5.0-259.0)	31.0 (7.0-1933.0)	0.320	25.5 (13.0-261.0)	23.0 (6.0-135.0)	0.682
Aspartate aminotransferase, U/L	29.5 (13.0-213.0)	26.0 (8.0-8191.0)	0.1031	35.5 (14.0-213.0)	34.0 (8.0-8191.0)	0.319	23.0 (13.0-198.0)	23.5 (9.0-244.0)	0.575
Blood urea nitrogen, mmol/L	4.5 (1.6-48.1)	4.1 (1.5-19.1)	<0.05	5.0 (2.3-48.1)	4.4 (1.5-19.1)	0.041	3.9 (1.6-9.4)	3.8 (1.7-13.7)	0.568
Creatinine, μ mol/L	71.7 (37.1-1299.2)	66.3 (35.9-9435.0)	0.062	71.7 (37.1-1299.2)	68.4 (35.9-9435.0)	0.245	72.0 (40.3-133.6)	63.4 (39.4-229.1)	0.265

Abbreviations: CNS, central nerves system.

P values indicate differences between patients with and without CNS. $P < 0.05$ was considered statistically significant

Table 4 Laboratory findings of COVID-19 patients with PNS symptoms

	Total			Severe			Non-severe		
	With PNS symptoms (n=19)	Without PNS symptoms (n=195)	<i>P</i>	With PNS symptoms (n=7)	Without PNS symptoms (n=81)	<i>P</i>	With PNS symptoms (n=12)	Without PNS symptoms (n=114)	<i>P</i>
Median (range)									
White blood cell count, $\times 10^9/L$	4.8 (2.8-7.5)	4.9 (0.1-20.4)	0.744	4.5 (3.1-6.8)	5.6 (0.1-20.4)	0.105	4.9 (2.8-7.5)	4.4 (1.8-14.0)	0.273
Neutrophil, $\times 10^9/L$	2.8 (1.5-5.4)	3.0 (0.0-18.7)	0.740	2.6 (1.5-5.3)	4.1 (0.0-18.7)	0.099	2.9 (1.9-5.4)	2.5 (0.7-11.8)	0.214
Lymphocyte count, $\times 10^9/L$	1.2 (0.6-2.6)	1.1 (0.1-2.6)	0.433	1.2 (0.6-1.6)	0.9 (0.1-2.6)	0.257	1.2 (0.7-2.6)	1.3 (0.4-2.4)	0.917
Platelet count, $\times 10^9/L$	204.0 (111.0-305.0)	213.0 (18.0-583.0)	0.564	204.0 (111.0-245.0)	205.0 (18.0-576.0)	0.558	214.5 (155.0-305.0)	219.0 (42.0-583.0)	0.806
C-reactive protein, mg/L	12.0 (3.1-81.0)	12.3 (0.1-212.0)	0.446	7.5 (3.1-76.4)	43.7 (0.1-212.0)	0.134	13.0 (3.1-81.0)	8.8 (0.4-126.0)	0.598
D-dimer, mg/L	0.4 (0.2-9.5)	0.5 (0.1-20.0)	0.399	0.5 (0.2-9.5)	1.3 (0.1-20.0)	0.272	0.4 (0.2-4.5)	0.4 (0.2-8.7)	0.989
Creatine kinase, U/L	67.0 (32.0-1214.0)	64.0 (8.8-12216.0)	0.413	105.0 (32.0-1214.0)	83.0 (8.8-12216.0)	0.761	66.0 (42.0-171.0)	57.5 (19.0-1260.0)	0.291

Lactate dehydrogenase, U/L	205.0 (2.5-517.0)	242.0 (2.2-908.0)	0.284	170.0 (46.0-517.0)	309.0 (2.2-880.0)	0.050	254.0 (2.5-481.0)	215.0 (2.9-908.0)	0.669
Alanine aminotransferase, U/L	26.0 (5.0-116.0)	27.0 (6.0-1933.0)	0.695	19.0 (5.0-80.0)	35.0 (8.0-1933.0)	0.232	26.0 (8.0-116.0)	23.0 (6.0-261.0)	0.555
Aspartate aminotransferase, U/L	22.0 (8.0-115.0)	27.0 (9.0-8191.0)	0.288	22.0 (8.0-53.0)	35.5 (12.0-8191.0)	0.126	22.0 (14.0-115.0)	23.5 (9.0-244.0)	1.000
Blood urea nitrogen, mmol/L	4.1 (1.6-8.8)	4.1 (1.5-48.1)	0.764	4.2 (3.5-8.8)	4.7 (1.5-48.1)	0.963	3.7 (1.6-5.3)	3.9 (1.7-13.7)	0.660
Creatinine, μ mol/L	62.5 (48.1-121.4)	68.3 (35.9-9435.0)	0.455	71.4 (58.3-121.4)	71.7 (35.9-9435.0)	0.717	59.9 (48.1-77.3)	66.6 (39.4-229.1)	0.235

Abbreviations: PNS, peripheral nerves system.

P values indicate differences between patients with and without PNS. *P*<0.05 was considered statistically significant.

Table 5 Laboratory findings of COVID-19 patients with muscle injury

	Total			Severe			Non-severe		
	With muscle injury (n=23)	Without muscle injury (n=191)	<i>P</i>	With muscle injury (n=17)	Without muscle injury (n=71)	<i>P</i>	With muscle injury (n=6)	Without muscle injury (n=120)	<i>P</i>
Median (range)									
White blood cell count, ×10 ⁹ /L	6.0 (2.3-20.4)	4.8 (0.1-15.6)	0.248	6.7 (2.3-20.4)	5.2 (0.1-15.6)	0.269	4.3 (2.4-6.1)	4.5 (1.8-14.0)	0.618
Neutrophil, ×10 ⁹ /L	4.3 (0.9-18.7)	2.9 (0.0-13.0)	0.031	5.5 (0.9-18.7)	3.5 (0.0-13.0)	0.076	2.6 (1.1-4.5)	2.6 (0.7-11.8)	0.945
Lymphocyte count, ×10 ⁹ /L	0.9 (0.1-2.6)	1.2 (0.1-2.6)	0.002	0.8 (0.1-2.6)	0.9 (0.1-2.5)	<0.05	1.2 (1.0-2.1)	1.3 (0.4-2.6)	0.846
Platelet count, ×10 ⁹ /L	185.0 (82.0-436.0)	215.0 (18.0-583.0)	0.224	182.0 (82.0-436.0)	209.0 (18.0-576.0)	0.407	223.0 (122.0-304.0)	219.0 (42.0-583.0)	0.688
C-reactive protein, mg/L	56.0 (0.1-212.0)	11.1 (0.1-204.5)	<0.001	70.8 (0.1-212.0)	21.0 (0.1-204.5)	0.078	18.1 (9.7-126.0)	8.1 (0.4-123.0)	<0.05
D-dimer, mg/L	1.3 (0.2-20.0)	0.5 (0.1-20.0)	<0.05	1.7 (0.2-20.0)	0.6 (0.1-20.0)	0.120	0.4 (0.2-1.3)	0.4 (0.2-8.7)	0.679
Creatine kinase, U/L	400.0 (203.0-12216.0)	58.5 (8.8-212.0)	<0.001	525.0 (203.0-12216.0)	64.0 (8.8-212.0)	<0.001	231.0 (206.0-1260.0)	57.5 (19.0-184.0)	<0.001

Lactate dehydrogenase, U/L	415.0 (147.0-743.0)	229.0 (2.2-908.0)	<0.001	442.0 (147.0-743.0)	285.0 (2.2-880.0)	<0.01	315.0 (210.0-666.0)	213.0 (2.5-908.0)	<0.05
Alanine aminotransferase, U/L	44.0 (14.0-173.0)	25.0 (5.0-1933.0)	<0.01	50.0 (14.0-173.0)	30.0 (5.0-1933.0)	<0.05	28.0 (16.0-63.0)	23.0 (6.0-261.0)	0.495
Aspartate aminotransferase, U/L	46.0 (22.0-209.0)	25.0 (8.0-8191.0)	<0.001	53.0 (26.0-209.0)	31.0 (8.0-8191.0)	<0.001	34.5 (22.0-60.0)	23.0 (9.0-244.0)	0.065
Blood urea nitrogen, mmol/L	4.8 (2.0-48.1)	4.1 (1.5-19.1)	<0.05	4.8 (2.4-48.1)	4.6 (1.5-19.1)	0.256	5.9 (2.0-10.6)	3.8 (1.6-13.7)	0.264
Creatinine, μ mol/L	80.5 (43.7-1299.2)	66.9 (35.9-9435.0)	<0.01	81.5 (43.7-1299.2)	68.4 (35.9-9435.0)	<0.05	77.4 (60.7-229.1)	65.1 (39.4-215.3)	0.050

P values indicate differences between patients with and without muscle injury. $P < 0.05$ was considered statistically significant.