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

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Abstract:	Summary Background: The outbreak of coronavirus disease 2019 (COVID-19) from Wuhan China is serious and has the potential to become epidemic unfortunately worldwide. We aimed to describe the neurological manifestations of patients with COVID-19. Methods: In this retrospective, observational study, we enrolled two hundred fourteen hospitalized patients with laboratory confirmed diagnosis of severe acute respiratory syndrome from coronavirus 2 (SARS-CoV-2) infection in three designated COVID-19 care hospitals of the Union Hospitals of Huazhong University of Science and Technology in Wuhan, China. Data were collected from 16 Jan- uary 2020 to 19 February 2020. Neurological symptoms fall into three categories: central nervous system (CNS) symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cere- brovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms (hypogeusia, hypos- mia, hypopsia, and neuralgia), and skeletal muscle injury. Data of all neurological symptoms were checked by two trained neurologists. Findings: 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 cere- brovascular 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%]). Interpretation Compared with non-severe patients with COVID-19, severe patients

	commonly had neurologic symptoms manifested as acute cerebrovascular diseases, impaired consciousness and skele- tal muscle injury. Funding: None.

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

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Summary

Background: The outbreak of coronavirus disease 2019 (COVID-19) from Wuhan China is serious and has the potential to become epidemic unfortunately worldwide. We aimed to describe the neurological manifestations of patients with COVID-19.

Methods: In this retrospective, observational study, we enrolled two hundred fourteen hospitalized patients with laboratory confirmed diagnosis of severe acute respiratory syndrome from coronavirus 2 (SARS-CoV-2) infection in three designated COVID-19 care hospitals of the Union Hospitals of Huazhong University of Science and Technology in Wuhan, China. Data were collected from 16 January 2020 to 19 February 2020. 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 muscle injury. Data of all neurological symptoms were checked by two trained neurologists.

Findings: 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%]).

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

Funding: None.

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 the disease as 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]. Some of them can adapt fast and cross the species barrier, such as 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 typical clinical manifestations including fever, cough, diarrhea, fatigue, and so on. 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 from January 16 to February 19, 2020 at three designated COVID-19 care hospitals of Union Hospitals of Huazhong University of Science and Technology. Two hundred fourteen hospitalized 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 Ethics Committee of Union hospital, 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, clinical symptoms, 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 skeletal muscular symptoms. Acute cerebrovascular disease included ischemic stroke and cerebral hemorrhage diagnosed by doing head CT. Skeletal 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 Wilcox rank-sum test. Proportions for categorical variables were compared using the $\chi 2$ 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 dis-

ease (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 nervons system symptoms: CNS (53 [24.8%]), PNS (19 [8.9%]) and skeletal muscle injury (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 skeletal 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 skeletal 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 skeletal muscle injury

Table 5 showed the laboratory findings of patients with and without skeletal 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 group, patients with skeletal 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 skeletal muscle damage (increased creatinine kinase levels). For non-

severe group, patients with skeletal muscle injury only had higher C-reactive protein and creatinine kinase levels compared with those without skeletal 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 skeletal muscle injury.

Therefore, we believe that this study would offer important new clinical information on COVID-19 that would help the clinicians raise awareness of its involvement of neurological system. It is especially meaningful to all to learn that for those with severe COVID-19, rapid clinical deterioration or worsening could be related to a neurological event such as stroke, which would contribute to its high mortality rate. Moreover, during the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, clinicians 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 muscles [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 injure 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 skeletal 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.

Contributors

BH, LM, HJ and YH conceptualized the paper. JC and XM analyzed the data with input from YL, MW, HJ, SC, QH, CH and YZ. BH, LM, HJ, MW and DW wrote the initial draft with all authors providing critical feedback and edits to subsequent revisions. All authors approved the final draft of the man-

uscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Data sharing

After publication, the data will be made available to others on reasonable requests to the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author and Union hospital, Tongji medical college, Huazhong university of science and technology.

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Table 1 Clinical characteristics of patients with COVID-19

	Total (n=214)	Severe (n=88)	Non-severe (n=126)	*P*
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
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<0.001

Data are presented as means ± standard deviations and n/N (%).
Abbreviations: CNS, central nervous system; PNS, peripheral nerves system
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

	Total (n=214)	Severe (n=88)	Non-severe (n=126)	*P*
White blood cell count, $\times 10^9$/L	4.9 (0.1-20.4)	5.4 (0.1-20.4)	4.5 (1.8-14.0)	<0.01
Neutrophil, $\times 10^9$/L	3.0 (0.0-18.7)	3.8 (0.0-18.7)	2.6 (0.7-11.8)	<0.001
Lymphocyte count, $\times 10^9$/L	1.1 (0.1-2.6)	0.9 (0.1-2.6)	1.3 (0.4-2.6)	<0.001
Platelet count, $\times 10^9$/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)	<0001
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 aminotransferase, 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, μmol/L	68.2 (35.9-9435.0)	71.6 (35.9-9435.0)	65.6 (39.4-229.1)	<0.05

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)	*P*	With CNS symptoms (n=27)	Without CNS symptoms (n=61)	*P*	With CNS symptoms (n=26)	Without CNS symptoms (n=100)	*P*
Median (range)									
White blood cell count, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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)	0.103	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, μmol/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 symptoms. $P< 0.05$ 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)	*P*	With PNS symptoms (n=7)	Without PNS symptoms (n=81)	*P*	With PNS symptoms (n=12)	Without PNS symptoms (n=114)	*P*
Median (range)									
White blood cell count, $\times10^9$/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, $\times10^9$/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, $\times10^9$/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, $\times10^9$/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, μmol/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 symptoms. $P<0.05$ was considered statistically significant.

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

	Total			Severe			Non-severe		
	With skeletal muscle injury (n=23)	Without skeletal muscle injury (n=191)	*P*	With skeletal muscle injury (n=17)	Without skeletal muscle injury (n=71)	*P*	With skeletal muscle injury (n=6)	Without skeletal muscle injury (n=120)	*P*
Median (range)									
White blood cell count, $\times10^9$/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, $\times10^9$/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, $\times10^9$/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, $\times10^9$/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, μmol/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 skeletal muscle injury. $P<0.05$ was considered statistically significant.