Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study

Jian Wu[1,2†], Jun Liu[3†], Xinguo Zhao[4†], Chengyuan Liu[5†], Wei Wang[2], Dawei Wang[6], Wei Xu[7], Chunyu Zhang[8], Jiong Yu[1], Bin Jiang[9], Hongcui Cao[1,10]*, Lanjuan Li[1]

[1]State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Rd., Hangzhou 310003, China;

[2]Department of Laboratory Medicine, The First People's Hospital of Yancheng City, Yancheng 224005, China;

[3]Department of Laboratory Medicine, The Fifth People's Hospital of Wuxi, Affiliated to Jiangnan University, Wuxi214005, China;

[4]Department of Respiration, The Fifth People's Hospital of Wuxi, Affiliated to Jiangnan University, Wuxi214005, China;

[5]Department of Infectious Disease, The First People's Hospital of Yancheng City, Yancheng 224005, China;

[6]Department of Infectious Disease, The second People's Hospital of Yancheng City, Yancheng 224001, China;

[7]Department of Preventive Medicine and Public Health Laboratory Sciences, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, China;

[8]Department of Laboratory Medicine, The second People's Hospital of Yancheng City, Yancheng 224001, China;

[9]Department of Laboratory Medicine, The Central Blood Station of Yancheng City, Yancheng224000, Jiangsu, China;

[10]Zhejiang Provincial Key Laboratory for Diagnosis and Treatment of Aging and Physic-chemical Injury Diseases, 79 Qingchun Rd, Hangzhou 310003, China.

† These authors contributed equally to this work

*corresponding author**:**

Hongcui Cao, M.D. State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Rd., Hangzhou 310003, China; Tel: 86-571-87236451; Fax: 86-571-87236459;

Email: hccao@zju.edu.cn

Summary

Compared with the cases in Wuhan, 80 imported cases of COVID-19 in Jiangsu Province exhibited mild or moderate symptoms and no obvious gender susceptivity, lower proportion of liver dysfunction and abnormal CT imaging and higher frequency nucleic acid detection.

Abstract

Background. We aimed to report the clinical characteristics of imported coronavirus disease-19 (COVID-19) in Jiangsu Province.

Methods. We retrospectively investigated the clinical, imaging, and laboratory characteristics of confirmed cases of COVID-19 with WHO interim guidance in three Grade ⅢA hospitals of Jiangsu from Jan 22 to Feb 14, 2020. Real time RT-PCR was used to detect the new coronavirus in respiratory samples.

Results. Of the 80 patients infected with COVID-19, 41 patients were female, with a median age of 46.1 years. Except for 3 severe patients, the rest of the 77 patients exhibited mild or moderate symptoms. 9 patients were unconfirmed until a third-time nucleic acid test. 38 cases had a history of chronic diseases. The main clinical manifestations of the patients were fever and cough, which accounted for 63 cases (78.75%) and 51 cases (-63.75%) respectively. Only 3 patients (3.75%) showed liver dysfunction. Imaging examination showed that 55 patients (-68.75%) showed abnormal, 25 cases (31.25%) had no abnormal density shadow in the parenchyma of both lungs. Up to now, 21 cases were discharged from the hospital, and no patient died. The average length of stay for discharged patients was 8 days.

Conclusions. Compared with the cases in Wuhan, the cases in Jiangsu exhibited mild or moderate symptoms and no obvious gender susceptivity. The proportion of patients having liver dysfunction and abnormal CT imaging was relatively lower than that of Wuhan. Notably, infected patients may be falsely excluded based on two consecutively negative respiratory pathogenic nucleic acid test results.

Keywords. Coronavirus disease-19 (COVID-19); clinical characteristics; imported cases; pneumonia

Introduction

The Coronavirus disease-19 (COVID-19) has been recently identified as a type of beta coronavirus.[1] They have enveloped virions that appear as round or oval, often polymorphous, with a diameter of 60-140nm.[2] It is widely distributed in human and other mammals, and its genome is more distant from severe acute respiratory syndrome coronavirus (SARS CoV) [3,4] and Middle East respiratory syndrome coronavirus (MERS CoV)[5,6]. Since December 2019, a large number of patients infected with COVID-19 have been reported in Wuhan, Hubei Province.[7-9] Most of them work in or live around the local South China seafood wholesale market, where wild animals are illegally on sale. Severe symptoms of acute respiratory infection appeared within the early stage of this pneumonia, with exacerbating cases where patients developed acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis and coagulation dysfunction that are difficult to correct.[10]

Up to February 14, 2020, 66,577 cases have been confirmed in China, including 54,406 cases in Hubei Province, 37,914 cases in Wuhan City, including medical staff, and several export cases in Thailand, Singapore, Japan, South Korea, the United States, Australia and other countries. Considering its highly epidemical nature, COVID-19 has been categorized as Class B infectious disease stipulated in the law of the People's Republic of China on the prevention and control of infectious diseases for the first time, and is managed as Class A infectious disease.[11]

So far, several studies have described the epidemiological and clinical characteristics of patients infected with COVID-19, but they are all limited to cases in Wuhan, but not in other areas.[12,13] In this study, the clinical characteristics of 80 patients diagnosed with COVID-19 in three Grade ⅢA hospitals of Jiangsu Province were discussed. We believe our findings will give further details to the epidemic situation and clinical characteristics of this novel coronavirus.

Patients and methods

Patients

All enrolled 80 patients, who were referred to the First People's Hospital of Yancheng City, the second People's Hospital of Yancheng City, and the Fifth People's Hospital of Wuxi from Jan 22 to Feb 14, 2020, were retrospectively and consecutively analysed. According to the arrangements by the Government, all three tertiary hospitals provide treatment for patients, in which all patients who were diagnosed as having COVID-19 according to WHO interim guidance.[14] We collected all the data including clinical, demographic, laboratory parameters, chest CT, length of hospitalization and intensive care unit (ICU) stay, and prognosis from patients' medical records and attending doctors. The data endpoint is Feb 14, 2020. The present study was performed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the First People's Hospital of Yancheng City. Written informed consent was obtained from participants or their families when data were collected retrospectively.

According to WHO Interim Guidance[14], the case in this study was defined as any one with epidemiological history and consistent with any two clinical manifestations and the pathogenic evidence:

1. Epidemiological history: (1) Within 14 days before the onset of the disease, there were tourism or residence histories of Wuhan or its surrounding areas, or other communities with confirmed cases; (2) Within 14 days before the onset of the disease, there were contacts with confirmed cases of COVID-19; (3) Within 14 days before the onset of the disease, there were contacts with suspected cases (having fever or respiratory symptoms) from Wuhan or its surrounding areas, or other communities with confirmed cases; (4) Aggregation: Within 14 days before the onset of the disease, one confirmed case was found in an enclosed environment (such as a family house, a construction site, an office, etc.), with one or more cases of fever respiratory tract infection were found at the same time, revealing potential interpersonal transmission or joint exposure of the disease.

2. Clinical manifestations: (1) Fever and/or respiratory symptoms; (2) Imaging indicates multiple mottling and interstitial changes in the lung periphery during the early stage, which subsquently developed into bilateral ground-glass opacity, infiltrates and lung

consolidation; pleural effusion was rarely seen; (3) In the early stage of the disease, the total number of leukocytes was normal or decreased, or the lymphocyte count was decreased.

3. Pathogenic evidence: Nucleic acid test was used to detect the new coronavirus in respiratory.

The patients were clinically classified as four types: mild, moderate, severe, and critically ill. The criteria for clinical classifications see supplementary Table S1.

Strategy for nucleic acid tests

Once a suspected case was admitted to the hospital, the nucleic acid test was carried out immediately. A nose swab and/or throat swab were taken from each patient. The nucleic acid test was considered positive if the result of either of the above samples was positive. If it was negative, the samples would be taken once a day for the next two days.

After the treatment, if the patient's condition improved significantly and there were no respiratory symptoms of fever or cough, the patient would be discharged after passing two consecutive nucleic acid tests.

Detection of coronavirus

150 μL of sample from throat swab and/or nose swab of each patient was used to extract total RNA. On the basis of the manufacturer's instructions, total RNA extracted using the respiratory sample RNA isolation kit (Zhongzhi, Wuhan, China) and each sample obtained 40 μl elution. In order to target the nucleocapsid (N) gene and open reading frame lab (ORF1ab) gene using a 2019-nCov nucleic acid detection reagent (Bio-germ, Shanghai, China), we use real-time RT-PCR with 5 μL RNA. The final reaction mixture concentration of primer and probe was 500 nm and 200 nm respectively. The sequences used and real-time RT-PCR performing conditions were listed in supplementary Table S2.

The lowest detection concentration is 1×10^3 copies / ml. There was no cross reaction with influenza A virus H1N1, H1N1 (2009), H3N2, H5N1, H7N9, influenza B virus (BV and BY types), human coronavirus (229E/HKU1/OC43/NL63/SARS/MERS), parainfluenza virus (1, 2, 3), rhinovirus A / B / C. No more than 50% blood and less than 0.9mg/ml of mucin in the sample will not cause interference.

Statistical analysis

Statistical analyses were performed with SPSS (v.18.0; SPSS Inc., Chicago, IL, USA). If the continuous measurement is a normal distribution, we present it as an average (SD); if it is not a normal distribution, we present it as a median (IQR); the classification variable is presented as a count (%). We also evaluated whether the laboratory parameters were outside the normal range.

Results

Demographics, baseline and clinical characteristics of patients infected with COVID-19

In this study, 80 cases infected with COVID-19 in Yancheng City and Wuxi City were investigated, including five families. All these cases were imported infections (with a history of epidemic in Wuhan) and had no contact with the seafood market in South China. None of these patients were medical staff. Among them, 41 patients (51.25%) were female, with a median age of 46.1 years (IQR 30.7-61.5). 27 patients (33.75%) were aged 25-49 years, 19 patients (23.75%) were aged 50-64 years, 15 patients (18.75%) were aged 18-24 years, 10 patients (12.50%) were under 18 years old, 9 patients (11.25%) were over 65 years old (Figure 1). Of the 10 patients under 18 years old, the minimum age was 4, 2 patients were between 6-8 years old, 6 patients were between 11-13 years old, the maximum age was 14. In term of clinical classification, 28 (35.00%) patients were mild type, 49 (61.25%) patients were moderate type, 3 (3.75%) patients were severe type and no patient was critically ill. During the diagnostic procedure, we found that 41 patients (51.25%) got a positive result in the first test, and 30 patients (37.50%) got a positive result in the second test. Surprisingly, another 9 patients (11.25%) remained negative until a third test. Of all the 80 patients, 38 cases (47.50%) had a history of chronic diseases, including cardiovascular and cerebrovascular diseases, endocrine system diseases, digestive system diseases, respiratory system diseases, malignant tumors and nervous system diseases (Table 1).

The most common symptoms were fever and cough, which accounted for 63 cases (78.75%) and 51 cases (63.75%) respectively. 30 cases (37.50%) had shortness of breath. In addition, 18 (22.50%) patients had muscle ache, 13 patients (16.25%) had headache and

mental disorder symptoms, and no patients had hemoptysis or diarrhea symptoms. The average time from onset to emergence of shortness of breath was 8.0 days (IQR 5.0-13.0). Except for 10 patients (12.50%) with acute respiratory injury and 2 patients (2.50%) with renal injury, there was no other organ damage (Table 1). The crossing points for positive detections alongside clinical characteristics were shown in supplementary Table S3.

Laboratory findings of patients infected with COVID-19

The white blood cell (WBC) count of 36 patients (45.00%) was lower than the normal range (4×10^9/L), and 26 patients (32.50%) had lymphocytopenia (the lymphocyte count was less than 1.0×10^9/L). 11 patients (13.75%) had platelets lower than the normal range (125×10^9/L), and no patients had platelets higher than the normal range (350×10^9/L). There were 62 patients (77.50%) with high C-reactive protein (CRP) and 59 patients (73.75%) with high erythrocyte sedimentation rate (ESR). Only 1 patient (1.25%) had elevated procalcitonin (PCT) level.

In terms of liver function, only 3 patients (3.75%) showed alanine transaminase (ALT) or aspartate aminotransferase (AST) above the normal range. Two patients (2.50%) had lower albumin level than the normal range (35 g/L). 18 patients (22.50%) had abnormal myocardial enzyme spectrum, indicating the increase of creatine kinase (CK). The level of lactate dehydrogenase (LDH) increased in 17 patients (21.25%). Two patients (2.50%) had different degrees of renal function damage, one of them had serious renal function damage (UREA: 26.5 mmol/L, CREA: 1054.4 mmol/L). The blood glucose (GLU) level of 19 patients (23.17%) exceeded the normal range (5.9 mmol/L). The level of D-dimer was increased in 3 patients (3.75%). Nine kinds of respiratory pathogens and influenza A and B nucleic acids were examined in all patients, and bacteria and fungi were cultured simutaneously. The results showed that all patients were negative for the pathogens above (Table 2).

Imaging features of patients infected with COVID-19

Of the 80 patients, 55 (68.75%) showed abnormal chest CT images, consisting 36 cases (45.00%) of bilateral pneumonia and 19 cases (23.75%) of unilateral pneumonia (Table 1). There were no bilateral lobular and subsegmental consolidation areas, bilateral ground glass shadows or subsegmental consolidation areas, only bilateral ground glass opacity (Figure 2A)

and unilateral ground glass opacity (Figure 2B). 25 cases (31.25%) had no abnormal density shadow in the parenchyma of both lungs (Figure 2C).

Treatment for patients infected with COVID-19

All patients were treated empirically with a single antibiotic, mainly moxifloxacin. The duration of antibiotic treatment was 3-12 days (median 7 days [IQR4-9]). All patients received ribavirin antiviral therapy for 3-12 days (median 7 days [IQR3-10]). 12 patients (14.63%) also received methylprednisolone sodium succinate or methylprednisolone for 3-12 days (median 5 days [IQR3-8]). 35 patients (43.75%) were managed with non-invasive ventilator (ie, face mask). No patient used invasive ventilator. One patient was supported with hemodialysis. In addition, three patients used traditional Chinese medicine (Jian Wei Xiao Shi oral liquid and Xi Yan Ping) to improve their gastrointestinal function.

The prognosis of patients infected with 2019-nCoV

Up to February 14, 21 of the 80 patients (23.75%) were discharged from the hospital. The average length of stay of discharged patients was 8 days. All other patients were still in the hospital for treatment, and no patient died. Discharge standard reference: body temperature returned to normal for more than 3 days, respiratory symptoms improved significantly, and respiratory pathogenic nucleic acid test was negative for two consecutive times (sampling interval at least 1 day).

Discussion

In this multi-center and multi-sample study, 80 cases infected with COVID-19 in Yancheng and Wuxi were reported. All patients were imported infections. Most of them received timely diagnosis and treatment as the government formulated an efficient early warning and isolation program in time. Except for 3 severe patients, the rest of the 77 patients exhibited mild or moderate symptoms. This report provided the latest information of infected patients in two cities of Jiangsu Province.

COVID-19 was mainly transmitted through respiratory droplets and contact.[15] At present, patients with COVID-19 are the main source of infection.[16] What's more remarkable

is that asymptomatic infections can also be a source of infection.[17] The two cities mentioned in this study, Wuxi and Yancheng, are respectively located in the South and North of Jiangsu Province, and they are representative in population, economic level and traffic level.

Compared with the results of the two studies on Wuhan cases by Chen et al[18] and Huang et al[19], we found that the gender proportion was equal in the 80 patients we included, contradicting to the conclusion that men were more susceptible than women. This may be related to the insufficient number of samples in all these three studies. The results may also be influenced by the spreading mode of the disease, as five cases of intrafamilial transmission were included in this study. The age distribution of the patients was consistent with the study by Huang et al[19].

In terms of clinical classification, 3 patients had severe pneumonia, and 77 patients had mild or moderate symptoms. These imported cases were timely diagnosed and treated in Jiangsu Province. Since most of the cases in this study were mild, the main symptoms were fever and cough. 10 patients had acute respiratory injury, 2 patients had renal injury, and no other organ damage was found.

In terms of laboratory tests, nearly half of the patients had a decreased number of WBC and one third of the patients had a decreased number of lymphocytes. In most patients, CRP level was elevated, but PCT level was normal. All these changes further illustrated that COVID-19 may exert a major impact on lymphocytes, especially T lymphocytes. The virus spreads and invades through respiratory mucosa, triggers a series of immune responses and induces cytokine storm *in vivo*, resulting in changes in immune components such as peripheral blood leukocytes and lymphocytes.[20] Therefore, intravenous immunoglobulins were used in most patients with decreased WBC and lymphocyte levels.

It has been reported that patients with COVID-19 infection are prone to exhibit liver dysfunction, and the potential mechanism is that COVID-19 may directly bind to ACE2 positive bile duct cells.[21,22] It is suggested that the liver abnormality of SARS and COVID-19 patients may not be caused by liver cell damage, but by bile duct cell dysfunction and other reasons. In our study, 3 patients had abnormal ALT and AST, and 2 patients had decreased protein level. In addition, 19 patients had elevated GLU level, and 18 patients had abnormal muscle zymogram.

In this study, all cases were confirmed by nucleic acid test. The sum of nucleic acid tests prior to a positive diagnosis for each patient was analyzed. Notably, 9 patients passed three tests before they got positive results. Therefore, we consider that if the suspected cases are excluded based on two consecutively negative respiratory pathogenic nucleic acid test results (the sampling time is at least one day apart), about 10% of the infected patients will be missed.

Chest imaging is of great significance for the diagnosis.[23] In the early stage, there were multiple mottling and interstitial changes, especially in the peripheral portion. In severe cases, lung consolidation can occur, but pleural effusion was rare. In the case reports of Wuhan, CT images of all patients were abnormal. 98% of the patients had bilateral involvement. However, in our study, the abnormal rate was relatively lower; 55 patients (68.75%) showed abnormal chest CT images, 36 (45.00%) showed bilateral pneumonia, 19 (23.75%) showed unilateral pneumonia. 25 cases had no abnormality on the first CT, and 23 of them had been diagnosed for more than 4 days. In this regard, we suggest that when screening patients, clinical manifestations, laboratory examination and chest imaging should be combined for comprehensive analysis.

Up to now, there is no specific drug for the treatment of patients with COVID-19.[24,25] A U.S. study showed that remdesivir had good therapeutic effect.[26] Now China has carried out preliminary clinical trials on this drug.[27] Currently, the clinical treatment mainly includes empirical antibacterial drugs, intravenous injection of ribavirin for antiviral, and appropriate dose of methylprednisolone to alleviate the shortness of breath. At the same time, it is suggested to use traditional Chinese medicine properly to improve the physical signs of patients. In this study, as there was no critical case, no patient used invasive ventilator. All three hospitals were followed the above scheme. At present, 21 cases have been discharged from the hospital with an average length of stay for 8 days, no death was reported, and all other patients were still in hospital.

This study is limited by its retrospective nature. First of all, due to the limited number of patients, our conclusions need to be further verified by large samples and multi-center data. Secondly, the prognosis is unavailable at the time of analysis, and extended follow-up time would provide more detailed information about potential risk factors that interfere with clinical outcomes. Third, only two cities in Jiangsu Province are selected in this study.

Although they are representative, more urban cases need to be included to make the research results more accurate.

To sum up, in-depth study is still needed for patients with COVID-19. Reliable rapid pathogen detection and practical differential diagnosis based on clinical description are crucial for clinicians to contact suspected patients for the first time, and it is urgent to develop virus vaccines and effective drugs.

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Figure legends

Figure 1: Number of age distribution, clinical classification, and nucleic acid tests of patients infected with COVID-19

(A) Number of confirmed patients by age group; (B) Number of confirmed patients by different clinical classification; (C) Number of nucleic acid tests used to confirm patients.

Figure 2: Chest x-ray images and chest CT images of three patients

(A) Chest x-ray images and chest CT images from a 71-year-old woman showing that there are scattered high-density shadows with fuzzy patches in the lower lobes of the two lungs, with ground glass like changes, with clear hilar structure, unobstructed trachea, no displacement of mediastinum, no enlarged lymph node shadow, and local thickening of bilateral pleura;

(B) Chest x-ray images and chest CT images from a 38-year-old man showing that there are small patchy ground glass like density increasing shadow in the upper and lower lobes of the left lung, with clear hilar structure, unobstructed trachea, no mediastinum displacement, no enlarged lymph node shadow, and no abnormality of pleura on both sides;

(C) Chest x-ray images and chest CT images from a 12-year-old boy showing that there was no abnormal density shadow in the parenchyma of both lungs, the structure of pulmonary hilus was clear, the trachea was unobstructed, mediastinum was not displaced, and no enlarged lymph node shadow was found.

Table 1. Demographics, baseline and clinical characteristics of patients infected with COVID-19

Variables	Patients (n=80)
Age(y)	
Mean(SD)	46.10 ± 15.42
Range	
<18	10(12.50%)
18-24	15(18.75%)
25-49	27(33.75%)
50-64	19(23.75%)
>=65	9(11.25%)
Sex	
Female	41(51.25%)
Male	39(48.75%)
Clinical classification	
Mild type	28(35.00%)
Moderate type	49(61.25%)
Severe type	3(3.75%)
Critically ill type	0(0.00%)
Types of infection	
Huanan Seafood Wholesale Market exposure	0(0.00%)
Imported infections	80(100.00%)
Number of nucleic acid tests	
The first time	41(51.25%)
The second time	30(37.50%)
The third time	9(11.25%)
Comorbidities	38(47.50%)
Cardiovascular and cerebrovascular	25(31.25%)
Endocrine system diseases	5(6.25%)
Digestive system disease	3(3.75%)
Respiratory system diseases	1(1.25%)
Malignant tumour	1(1.25%)
Nervous system diseases	1(1.25%)
Chronic kidney disease	1(1.25%)
Chronic liver disease	1(1.25%)
COPD	0(0.00%)
HIV infection	0(0.00%)
Septic shock	0(0.00%)

Table 1 continued

Variables	Patients (n=80)
Signs and symptoms at admission	
Fever	63(78.75%)
Cough	51(63.75%)
Shortness of breath	30(37.50%)
Muscle ache	18 (22.50%)
Headache and mental disorder symptoms	13 (16.25%)
Sore throat	11(13.75%)
Rhinorrhoea	5(6.10%)
Chest pain	3(3.75%)
Diarrhoea	1(1.25%)
Nausea and vomiting	1(1.25%)
More than one sign or symptom	66(82.50%)
Chest x-ray and CT findings	
Bilateral pneumonia	36 (45.00%)
Unilateral pneumonia	19 (23.75%)
No abnormal density shadow	25 (31.25%)
Treatment	
Antibiotic treatment	73(91.25%)
Antiviral treatment	80(100.00%)
hormone therapy	12(14.63%)
Intravenous immunoglobulin therapy	16(20.00%)
Non-invasive(ie,face mask)	35 (43.75%)
Mechanical ventilation	0(0.00%)
ECMO	0(0.00%)
Traditional Chinese medicine	3(3.75%)
Clinical outcome	
Remained in hospital	61(76.25%)
Discharged	21(23.75%)
Died	0(0.00%)

Abbreviation: Coronavirus disease-19 (COVID-19); COPD, chronicobstructivepulmonary disease; ECMO, extracorporeal membrane oxygenation.

Table 2. Laboratory findings of imported patients infected with COVID-19

Variables	Normal range	Patients (n=80)		
		Median (IQR)	Increased No.(%)	Decreased No.(%)
Blood routine				
White blood cell count (× 10^9/L)	3.5-9.5	4.1(3.2-5.7)	5 (6.25%)	36 (45.00%)
Neutrophil count (× 10^9/L)	1.8–6.3	4.3(2.3-5.9)	20 (25.00%)	-
Lymphocyte count count (× 10^9/L)	1.1–3.2	0.6(0.4-1.0)	-	26 (32.50%)
Monocyte count count (× 10^9/L)	0.1-0.6	0.5(0.3-0.7)	15 (18.75%)	-
Platelet count count (× 10^9/L)	125.0–350.0	155(116-188)	0(0.0%)	11 (13.75%)
Haemoglobin (g/L)	130.0–175.0	125.3(13.4)	-	29 (36.25%)
Coagulation function				
Activated partial thromboplastin time (s)	21.0–37.0	18.6(17.2-28.6)	-	2 (2.50%)
Prothrombin time (s)	10.5–13.5	10.8(9.3-13.2)	-	3 (3.75%)
D-dimer(μg/L)	0.0–1.5	0.9(0.4-2.4)	3 (3.75%)	-
Blood biochemistry				
Alanine aminotransferase(U/L)	9.0-50.0	24(12-38)	3 (3.75%)	-
Aspartate aminotransferase(U/L)	15.0-40.0	30(19-39)	3(3.75%)	-
Albumin(g/L)	40.0–55.0	38.3(37.0-46.2)	-	2 (2.50%)
Total bilirubin(μmol/L)	0.0–21.0	6.6(5.4-12.0)	1(1.25%)	-
Blood urea nitrogen(mmol/L)	3.6-9.5	4.9(3.4-5.9)	2 (2.50%)	-
Serum creatinine(μmol/L)	57.0-111.0	78(60-90)	2 (2.50%)	-
Lactate dehydrogenase(U/L)	120.0-250.0	226(182-308)	17 (21.25%)	-
Glucose(mmol/L)	3.9–6.1	6.8(4.6-7.7)	19 (23.17%)	-
Creatine kinase (U/L)	50.0–210.0	99(61-191)	18 (22.50%)	-
Creatine kinase–MB(U/L)	<25	22(15-25)	16 (20.00%)	-
Infection-related biomarkers				
C-reactive protein≥5.0(mg/L),No.(%)	0.0–5.0	6.6(5.3-12.3)	62 (77.50%)	-
Procalcitonin≥5.0 (ng/mL),No.(%)	0.0–5.0	1.3 (0.4-2.6)	1(1.25%)	
Erythrocyte sedimentation rate≥15 (mm/h),No.(%)	0.0-15.0	11.9(9.0-17.2)	59(73.75%)	-

Abbreviation: Coronavirus disease-19 (COVID-19); IQR, interquartilerange.

Figure 1

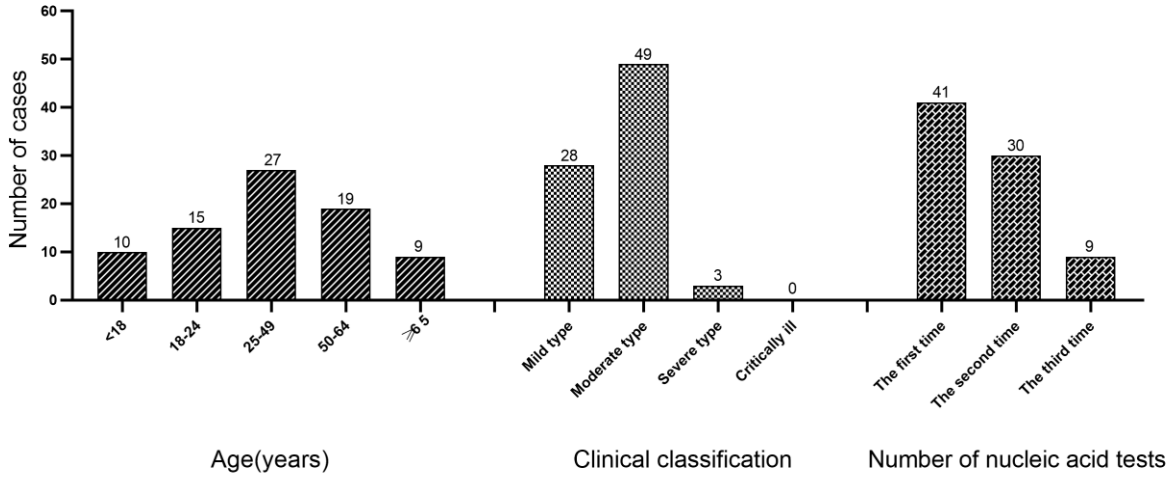

Figure 2