Clinical characteristics of pneumonia patients of long courses infected with SARS-CoV-2

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Research

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Abstract

Background: Since December, 2019, Wuhan, China, has experienced an outbreak of 2019 novel coronavirus pneumonia (COVID-19). Epidemiological and clinical characteristics of patients with COVID-19 have been reported. A few studies reported clinical course of illness of median 22 days, including viral shedding of median 20 days, but there are several cases with a longer time of viral shedding.

Methods: In this retrospective, single-centre cohort study, we included four cases with a longer course of illness of more than 40 days with laboratory-confirmed COVID-19 from Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or still in hospital by March 15, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records. We describe the epidemiological and clinical characteristics and the course of viral shedding.

Results: Of the four patients, one was discharged and the other three were still in hospital. Two patients had comorbidity, one with hypertension and one with diabetes. We found smoking is not an independent risk factor. And D-Dimer maybe relates to severity of illness but not course of illness. Decreased lymphocyte count had a slow recovery process in three patients. elevated eosinophils count in all patients suggest maybe elevated eosinophils count was a reason of long course. Nucleic acid detection suggests maybe more sampling sites represent more virus replication sites and longer course illness.

Conclusion: In this study we find some non-critical severe relatively young patients with sustained non-negative with nucleic acid detection whose character is different from former studies described. Of course, it needs much more cases to further study. It's hoped to provide strategy of isolation of infected patients and optimal antiviral interventions in the future.

Background

In December 2019, a novel atypical pneumonia caused by the 2019 novel coronavirus (2019-nCoV) was reported in Wuhan, China[1]. As of March 15, 2020, there were 80860 confirmed cases in China, including 3213 deaths reported by Chinese government. Now it is reported an outbreak of 2019-nCoV all over the world. It not only caused thousands of families huge psychological trauma but brought huge economic burden for all over the world. Most pathogenic to humans' coronaviruses had mild clinical symptoms[2], except severe acute respiratory syndrome coronavirus (SARS-CoV)[3] and Middle East respiratory syndrome coronavirus (MERS-CoV)[4]. The 2019-nCoV pathogen is confirmed closely related to SARS-CoV[5].

Homology modelling revealed that 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV, 2019-nCoV might use ACE2 as the receptor[6], and it binds ACE2 with higher affinity than SARS-CoV[7]. There are some amino acid mutations in the 2019-nCoV receptor-binding domain. Studies also suggested that high expression of ACE2 may increase susceptibility to infection[8]. The 2019-nCoV showed interesting, new phenomena. for example, there were some asymptomatic infections. some

patients discharged from hospital were tested positive again by real-time RT-PCR assay of nasal and pharyngeal swab specimens from the upper respiratory tract. In addition, some patients with long courses of illness were continually non-negative with acid confection. some scholars suggest it is a chronic infectious disease and the virus may coexist with human like HIV and HBV.

Previous study showed the median duration of viral shedding was 20 days (interquartile range (IQR) 17-24) with the longest duration of 37 days. The duration varied for patients with different health conditions, in critical severe patients, it was 24 days(IQR22-30) and 19 days (IQR 17-22) in severe patients, and moderate patients even shorter[9]. In addition, long duration of disease/viral shedding is usually observed in patients with older age or underlying medical conditions[9]. in this study we demonstrate four younger patients (≤ 50 years old), with a good health condition, having a long viral shedding of ≥ 40 days. We aim to provide the instruction to assess the risk of transmission and the isolation duration of patients.

Methods

Study design and participants

In this study, we collected four patients no more than 50 years old, with a good health condition, a long course of disease/viral shedding (≥ 40 days) admission to hospital from January 6 to February 17, and as to March 15, 2020 at Wuhan Pulmonary Hospital, Wuhan, Hubei, China. Patients were diagnosed as having 2019-nCoV pneumonia on the basis of the World Health Organization (WHO) interim guidance[10]. The viral target fragments of 2019-nCoV specific nucleic acid detection technology are viral ORF1ab and N genes. The study was approved by Ethics Commission of Xinhua Hospital affiliated to Shanghai Jiaotong University. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Procedures

We obtained general information, clinical, treatment, and outcome data from patients' medical records. All data were entered and checked by two physicians. The date of disease onset was defined as the day when the first symptom was noticed. the course of disease is calculated using the date of obtaining two consecutive negative test results using nucleic acid based detection minus the date of disease onset.

A confirmed case of Covid-19 was defined as a positive result on real-time RT-PCR assay of nasal and pharyngeal swab specimens from the upper respiratory tract. Only laboratory-confirmed cases were included in the analysis. All patients had chest computer tomography (CT) scan. Patients were diagnosed as severely ill if at least one of the following symptom was reported: 1) distress of respiratory with respiratory rate $\geq 30/\text{min}$; 2)Oxygen saturation $\leq 93\%$ in the rest state, and 3)arterial oxygen tension (PaO_2) over inspiratory oxygen fraction (FIO_2) of less than 300 mm Hg.

Outcomes

The primary end point was discharge from hospital.

Results

Demographic data and clinical symptoms

The demographic and clinical characteristics Of the 4 patients were summarized in Table 1. Case 1 was a 33 years old female without underlying comorbidities. The patient had no exposure to Huanan Seafood Market, which was linked to the first reported COVID-19 case. her first symptoms were cough and dizziness. the temperature was no more than 38°C in her later disease course. She was diagnosed as moderate pneumonia and still in hospitalization at the end of our data collection. her illness courses exceeded 40 days.

Case 2 was a 50 years old female with hypertension. She had Covid-19 exposure because of her physician occupation. The first symptom were cough, sore throat and myalgia. Her body temperature is no more than 38°C in all through her illness courses. She was diagnosed as moderate pneumonia, and her illness courses was 40 days. She was discharged from hospital at day 40.

Case 3 who was 36 years old without underlying comorbidities, male, had confirmed Covid-19 pneumonia patients exposure because of his physician occupation, his first symptom is cough, and fever, and later diarrhea. his highest body temperature is up to nearly 40°C before admission to hospital. He was diagnosed as severe pneumonia, and his illness courses was more than 40 days. She was still in hospital.

Case 4 who was 46 years old with diabetes, male, had Huanan Seafood Market exposure, his first symptom is cough and chest tightness, and later short of breath. his highest body temperature is 37.7°C before admission to hospital. He was diagnosed as severe pneumonia, and his illness courses was more than 50 days. He was still in hospital. The body temperature alteration of four cases was shown in figure 1.

Nucleic acid tests

All nucleic acid test results and the corresponding sampling sites of the 4 patients were shown in Figure 2. All cases had both double-negative and double-positive result at different time during the disease course. It is worth noting that sampling sites of case 2 were stool, sputum and throat swab specimens, while the other three cases were sampled from throat swab specimens. Case 3 and case 4 also were tested blood antibody. Case 2 had two consecutive double-negative results and was discharge from hospital, while other three cases were still in hospital.

Laboratory tests

Laboratory values are shown in Figure 3. Two moderate pneumonia cases (1 and 2) had no elevated D-Dimer level, while two severe cases (3 and 4) had elevated D-Dimer. This is confirmed former studies result of the severity of disease is related to D-Dimer level. Case 2, 3 and 4 had decreased lymphocyte count. Case 3 had the largest reduction of 0.15×10^9 . This patient also had constantly higher

temperatures, whether it suggests the body temperature is related to lymphocyte count needs further confirmation. All four cases had elevated eosinophils count. and the marker reached the highest level in the days 25-30, followed by a slow decrease, with more fluctuation in case 3 and 4, first reduced lower than normal, even zero the lowest in about days 10, and increase slowly, to the highest in the days 25-30, subsequently decrease slowly. Whether it suggests a reason of long courses needs more data to confirm. Increased neutrophil occurred in case3 and case4. The elevation of HCRP was also observed in case3 and case4. These two cases had secondary bacterial infection following virus infection. Maybe it suggests the secondary bacterial infection has an influence on severity of disease, but if secondary bacterial infection exists has no relation to the course of illness. From the data of hemoglobin, we observed the two severe cases had no anemia, while the decreased hemoglobin of two moderate cases was observed. It suggests the decreased hemoglobin has no relation to the course of illness. Elevated lactate dehydrogenase (LDH) was found in two severe cases, while decreased lactate dehydrogenase was found in case2. It maybe suggests the elevated LDH is related to severity of disease, but had no effect on the course of illness. Lymphocyte/ Neutrophil data shown the lower level in two-three weeks, and return to normal slowly after 3 weeks.

Imaging examinations

Intact CT imaging of all cases are available. Features of CT imaging, including location, proportion, numbers of associated lung lobes and manifestation, were shown in the supplementary table. Ground-glass opacity in both lungs were characteristically observed on CT in three cases without case1. Peripheral distribution was observed in case 1, and bilateral sides involvement were observed in other three patients. Pleural effusion and thickened pleura was not detected in any case(Figure 4).

Treatment

Antiviral drugs, Mechanical ventilation, Immunotherapy, oxygen therapy were administered to all patients. Intravenous antibiotics and Corticosteroids were given to two severe patients (Figure 5). Traditional medicine was given to two moderate pneumonia. During the course of illness, case4 were given two antiviral drugs: Arbidol, Lopinavir and Ritonavir Tablets, two antibiotics: moxifloxacin, Levo +AG1:Al3 floxacin, 18 days of corticosteroids in all. Elevated ALT level was only observed in case4 . Case2 was given three antiviral drugs: Arbidol, Lopinavir and Ritonavir, oseltamivir, and Chinese traditional medicine. And only case2 had drug caused leukopenia. Viral infection is a kind of self-limiting disease, although many things of the novel Covid-19 pneumonia is not clear, if it suggests the over-treatment of these patients needs consideration.

Complications and outcome

Until now, only case2 was discharged from hospital after two consecutive double-negative result. The other three cases were still in hospital. The two severe cases had hypoalbuminemia, case4 had respiratory failure. All four cases had no exacerbation.

Discussion

2019-nCoV is a novel coronavirus, it can be detected in the gastrointestinal tract, saliva, urine, but there are still many things unclear, including how the virus is transmitted from person to person, whether the virus can be spread by the faecal-oral route, how does the virus replicate in different sites? And whether that relate to the severity of disease? if nucleic acid based detection exist false positive and negative, how much is the false positive or negative rate of nucleic acid detection, and why some patients are sustained non-negative with nucleic acid based detection.

Previous research confirmed older patients with co-morbidities seem to be easily developing severe disease, and the detectable 2019-nCoV RNA persisted for median 20 days, prolonged virus shedding was associated with fatal outcome[9]. In this study we find several young patients no more than 50 years old, and have a better basic physical condition, while their prolonged virus detection was more than 40 days, the disease type was moderate or severe. And all survival. We found the doctor and the nurse of the four patients have clear contact with confirmed patients. As a typical RNA virus, the average evolutionary rate for coronaviruses is roughly 10^{-4} nucleotide substitutions per site per year, with mutations arising during every replication cycle[2], and if this suggests there are different mutations co-exist in the same patient, this needs deep observation and sequence detection.

Although it is reported the number of deaths associated with 2019-nCoV have a lower case fatality rate than either SARS-CoV or MERS-CoV, The transmission is much more rapid than SARS-CoV or MERS-CoV[11, 12], and patients suffered from 2019-nCoV were 10 times more than SARS-CoV. The duration of infectious virus replication is important to assess the risk of transmission and the isolation duration of patients. To ease the tension of hospital and health workers, it needs to study the non-severe young patients of long course. Previous studies confirmed the detectable 2019-nCoV persisted for a median of 20 days in survivors, but in this study we find some survivors the detectable 2019-nCoV persisted for more than 40 days. Some scholars suggest 2019-nCoV is a chronic disease like HBV, but from the current evidence and discharge patients, the result of 2019-nCoV is a chronic illness like HBV is not sufficient. It needs further study. We tend to the view of self-limiting acute infectious disease. As to the longer course of illness needs further information and study.

Based on the expression of ACE2 in smoking individuals, it is inferred that long-term smoking might be a risk factor for 2019-nCoV[13], and in this study, We showed the evidence against that finding. Therefore, the association between smoking history and COVID-19 might require further investigation.

From the data of nucleic acid detection, we observed one patient may be double-positive with nucleic acid detection from different secretions. It suggests more sampling sites represent more virus replication sites and longer course illness. It also needs further study.

Limitations

For provide information quickly, we first introduce four representative patients of long course of illness in this study, and later we will provide more cases of long course. The virus contected was not quantitative, so we can't confirm if the course of illness is associated with the virus concentration.

Conclusions

In conclusion, in this study we find some non-critical severe relatively young patients with sustained no-negative with nucleic acid detection. It will provide strategy of isolation of infected patients and optimal antiviral interventions in the future.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

GX Chen and X Lan collected the data, LY Huang and WW Lu accomplished data analysis, L Wang, CL Wang, LY Huang, WW Lu and GW Zeng performed imaging processing, CL Wang drafted the manuscript and made literature review, L Yang, YY Cai and H Huang designed the study and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Ethics approval and consent to participate

This study was approved by the Ethical approval was received from the Ethics Committee of Xinhua Hospital affiliated shanghai jiaotong University school of medicine (approval number: XHEC-D-2020-042).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Clinical Characteristics of the Study Patients				
Characteristic	Case1	Case2	Case3	Case4
Age,years	33	50	36	46
Sex	Female	Female	Male	Male
Profession(Doctor or Nurse)	No	Yes	Yes	No
Huanan Seafood Market Exposure	No	No	No	Yes
Smoking	No	No	No	No
Comorbidities	None	Hypertension	None	Diabetes
Fever before admission(highest)	36.5°C	36.8°C	39.7°C	37.7°C
Fever during hospitalization(highest)	37.9°C	37.4°C	38.9°C	37.8°C
SpO2 during hospitalization(lowest)(%)	95	94	89	79
FiO2	0.33	0.33	0.41	0.45
Symptoms				
Cough	Yes	Yes	Yes	Yes
Expectoration	No	Yes	Yes	No
Shortness of breath	No	Yes	Yes	Yes
Debility	No	No	Yes	No
Myalgia	No	Yes	No	No
Sore throat	No	Yes	No	No
Nasal congestion	Yes	No	No	No
Headache	Yes	No	No	No
Chest tightness	No	No	No	Yes
Palpitation	No	Yes	Yes	No
Diarrhea	No	No	Yes	No
Onset of symptom to Hospital to admission, days	9	3	9	8
Course of illness, days	>40	40	>40	>50
Classification	Common	common	severe	severe
Outcome	in-hospital	discharge	in-hospital	in-hospital
Complication				
Respiratory failure	No	No	No	Yes
Leukopenia	No	Yes	No	No
treatment				
oxygen therapy	Yes	Yes	Yes	Yes
Non-invasive assisted ventilation(BIPAP)	No	No	No	Yes
Antiviral drug	Yes	Yes	Yes	Yes
Antibiotics	Yes	No	Yes	Yes
Corticosteroids	No	No	Yes	Yes
Immunotherapy	Yes	Yes	Yes	Yes
Chinese traditional medicine	Yes	Yes	No	No

Figures

Figure 1

Body temperature alteration of four patients.

Figure 2

Disease/virus shedding based on nucleic acid detection of four patients.

Figure 3

Laboratory values of four patients. A. Levels of D-dimer of four patients. B. Lymphocyte count of four patients. C. Eosinophils count of four patients. D. Neutrophil(%) of four patients. E. HCRP of four patients. F. Hemoglobin of four patients. G. LDH of four patients. H. Lymphocyte/ Neutrophil of four patients.

Figure 4

Chest CT images of four patients. A. Transverse chest CT image from case1 showing slight ground-glass opacity in the left lower lobe area on day 5 after symptom onset. B. Transverse chest CT image from case2 showing bilateral multiple patchy shadows with uneven density and unclear borders on day 7 after symptom onset. C. Transverse chest CT image from case3 showing bilateral multiple large diffuse ground-glass opacity on day 11 after symptom onset. D. Transverse chest CT image from case4 showing bilateral multiple large diffuse ground-glass opacity with obvious outer lateral distribution on day 11 after symptom onset.

Figure 5

Clinical Course and treatment (FIO2 denotes fraction of inspired oxygen, PEEP positive end-expiratory pressure).