New perspectives into the clinical characteristics of COVID-19 disease

Chun Liu
Department of Critical Care Medicine, Dazhou Central Hospital, Sichuan Province, China
FanXin Zeng
Clinical Research Center, Dazhou Central Hospital, Sichuan Province, China
PingXi Wang
Science and Education, Dazhou Central Hospital, Sichuan Province, China
HuaPing Wu
Science and Education, Dazhou Central Hospital, Sichuan Province, China
ShuKai Deng
Department of Respiratory Medicine, Affiliated Hospital of Southwest Medical University, Sichuan Province, China
JinPing Liu
Dazhou Vocational College of Traditional Chinese Medicine, Sichuan Province, China
Dan Liu
Department of Respiratory Medicine, Affiliated Hospital of Southwest Medical University, Sichuan Province, China
Qiang Gao
Department of Critical Care Medicine, Dazhou Central Hospital, Sichuan Province, China
ChunFeng Xiang
Imaging Center, Dazhou Central Hospital, Sichuan Province, China
FanWei Zeng (109284521@qq.com)
Clinical Research Center, Dazhou Central Hospital, Sichuan Province, China
XiangDe Zhen (zxdfq123@163.com)
Department of Critical Care Medicine, Dazhou Central Hospital, Sichuan Province, China

Research Article

Keywords: COVID-19, demographic, clinical, and laboratory data, fecal nucleic acid positive

Posted Date: April 22nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-24315/v1

Abstract

COVID-19 has become a global pandemic, but with very little is known about it. In this single-centered, retrospective study, we collected all 37 confirmed cases of COVID-19 diagnosed in Dazhou, Sichuan, China from January 23 to February 25, 2020 and analyzed the demographic, clinical, and laboratory data. All of the cases were either imported from Wuhan and transmitted in family clusters. The average age of the patients was 45.76 ± 13.1 years. The average duration of pharyngeal swabs was 20.65 ± 6.7 days. Four (10.8%) patients were asymptomatic, 33 (89.1%) patients had increased lactic acid, 17 (45.9%) patients had increased fibrinogen C (Fib-C), and 5 (13.5%) patients had increased D-Dimers. 29 (87.9%) cases were positive for new coronavirus-specific antibodies, 4 (10.8%) cases were positive for viral nucleic acid in stool samples, 1 (2.7%) patient had positive culture of Klebsiella pneumonia. Therefore, we can predict that Lopinavir/ritonavir and abidol may not be effective in treating COVID-19.Elevated lactic acid, Fib-C, and D-dimer in patients may be predictors of disease progression. The new coronavirus-specific IgM and IgG antibodies can help to diagnose the disease. We need to pay attention to the risks posed by fecal nucleic acid positive patients.

Authors Chun Liu, FanXin Zeng, and PingXi Wang contributed equally to this work.

Introduction

In December 2019, a novel Coronavirus 2019 (COVID–19) caused by severe respiratory syndrome coronavirus 2 (SARS-CoV–2) broke out first in Wuhan, China. On March 11, 2020, the World Health Organization declared COVID–19 a pandemic. Further, as of March 15, 2020, WHO reported that more than 100 countries had been affected by the COVID–19 pandemic with about 153,517 confirmed cases and 5,735 deaths (*https://www.who.int/#)*.. Previous studies have recognized some clinical

characteristics of COVID–19 including the median incubation period estimated to be 4 days (interquartile range, 2 to 7)[1] and the most common symptoms are fever, cough, shortness of breath, muscle pain, headache, chest pain, nausea, vomiting, and diarrhea in some patients. Chest CT mainly manifests as large patches in both lungs and ground-glass opacity. The disease rapidly progresses to acute respiratory distress syndrome (ARDS) and multiple organ failure which results in death.[2] However, during the treatment process, we discovered some new challenges that need to be addressed.

Results

The study included 37 patients diagnosed with COVID–19, out of which 13 (35.1%) patients had a clear history of exposure to Wuhan, and the 24 patients were imported second-generation cases. The average age of the patients was 45.76±13.1 years and the maximum age was 82 years. The gender representation of the patients was 56.8% male and 43.2% female. The average duration of pharyngeal swabs was 20.65±6.7 days. Four (10.8%) patients were asymptomatic who were all females and the duration of nucleic acid positive in asymptomatic infections was 11–35 days (table 1).

Nucleic acid positive time calculation method: first nucleic acid positive time to second nucleic acid negative time (Diagnosis and treatment of new coronavirus pneumonia in China (Trial version 6)).

Elevated admission lactate was reported in 33 (89.1%) patients, 17 (45.9%) patients had elevated Fib-C, and 5 (13.5%) had elevated D-dimers. Based on the new coronavirus-specific antibodies (Using the colloidal gold method, Guangzhou Wanfu Biotechnology Co., Ltd., production license number: 20030645), a total of 33□4 patients did not do this test□ cases were tested, out of which 29 (87.9%) tested positive and 4 (10.8%) were positive for stool nucleic acid (Table 2).

During hospitalization, screening of all the patients for influenza A virus (H1N1, H3N2), influenza B virus, respiratory syncytial virus, and adenovirus antigen/antibody was performed. All the patients tested negative for all the above viruses but showed lung consolidation. Patients with significantly elevated infection parameters had a sputum culture. Only 1 (2.7%) of the patients had developed Klebsiella pneumonia with no history of concomitant disease. However, the patient improved after antibiotic treatment (Table 3).

Among all the COVID–19 confirmed patients, 35 (94.6%) patients were treated with alpha-interferon nebulization combined with abidol or lopinavir/ritonavir antiviral therapy. A total of 12 (32.4%) patients were treated with Abidol and 23 (62.2%) patients with lopinavir/ritonavir. Elevated infection parameters (leukocyte, C-reactive protein, or calcitonin source) or positive sputum culture were reported in 7 (18.9%) patients. For patients with lower lymphocytes and longer nucleic acid positive duration, human immunoglobulin 10g/d was administered for 3–5 days. Only a few patients experienced a transient increase in transaminase and poor appetite during antiviral treatment. Since COVID–19 is a new infectious disease with the rapid transmission, psychological intervention is also necessary for some patients who may develop anxiety and depression. A total of 4 (10.8%) patients received the psychological intervention (table 4).

By comparing the number of cloudy days of nucleic acid in patients treated with lopinavir/ritonavir and abidol, it was found that $P>0.05$, neither of which was statistically significant (table 5).

Typical imaging features from one of the patients with diabetes and the new coronavirus pneumonia were collected(Figure 1). At the onset, the ground-glass opacity of both lungs progressed rapidly and gradually changed. This suggested an increase in exudation in both lungs, reaching a peak of exudation at about 15 days. The entire course of this patient's covid–19 was 2 months.

Discussion

Coronavirus is an enveloped positive-sense RNA virus, belonging to the Coronaviridae and segment-free virus families[3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) is among the seven coronaviruses that can infect humans. The other six coronaviruses include HCoV–229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1. SARS-CoV and MERS-CoV3. SARS-CoV–2, SARS-CoV, and MERS-CoV3 are highly pathogenic and can cause severe human respiratory syndrome, and the other four causes mild

upper respiratory disease[4–8]. The mortality of SARS CoV has been reported to be more than 10% and MERS CoV at more than 35%[9–10]. However, the SARS-CoV–2 mortality rate is currently estimated at 2–5%[11].

Previous studies have reported the clinical characteristics and treatment strategies for patients infected with SARS-CoV–2. SARS-CoV–2 can cause coagulopathy and even death[12]. Among COVID–19 patients, 5 (13.5%) patients had elevated D-dimer, and 17 (45.9%) patients had elevated Fib-C. The increase in Fib-C indicated possibilities of blood coagulation, therefore, there is a need to pay close attention to the risk of deep vein thrombosis[13–14]. Elevated D-dimer is often used as an indicator of pulmonary embolism, but it can also be elevated in inflammatory diseases. Studies by Han[15–16] et al, reported that patients with severe SARS-CoV–2 infection had higher D-dimer. In mild patients, monitoring of the D-dimer values may help in the early detection of severe cases. Gao Y[17] et al, proposed that D-dimer has important clinical value in early prediction of the severity of COVID–19.

The increase in lactic acid is often caused by anaerobic fermentation. We found that 33 (89.1%) patients had increased lactic acid which was mainly accumulated in the lungs. We speculated that in the early stages of the disease, patients experience different levels of hypoxia due to lung infiltration or fever. Therefore, there is a need to correct the hypoxia in COVID–19 patients in a good time. Peng YD[18] and others also found that lactic acid accumulation and thrombosis can exacerbate the risk of death in COVID–19 patients. Therefore, we advocate for close monitoring of the patients' lactic acid, internal environmental conditions, and hypoxia to prevent the disease from aggravating to multiple organ failure and even death.

Generally, IgM can be produced 3–5 days after exposure to pathogenic microorganisms. IgG usually appears after IgM and can persist for many years after the infection. In this study, 33 patients confirmed to have COVID–19 were tested, and 29 (87.9%) were positive or weakly positive. However, Li et al[19] tested patients for IgM and IgG antibodies in 25 COVID–19 confirmed patients. They found 96% clinical sensitivity and 100% specificity of the tests. Therefore, detection using the new coronavirus IgM and IgG antibodies can complement the inadequacies presented by the nucleic acid detection methods.

Some new challenges currently being faced were identified in this study. For example, among the 37 COVID–19 patients, 4 (10.8%) patients had positive nucleic acid in the stool. Zhang J et al[20–22] also reported a small number of cases with positive nucleic acid in stool. One of the patients tested positive for viral nucleic acid in the stool for more than 40 days, and 2 patients experienced intermittent abdominal pain. Therefore, we recommend that the virus in the stool should be isolated and cultured from the patient to further confirm the existence of fecal-oral transmission. This will help to provide additional effective measures for the public against the spread of COVID–19.

Psychological problems caused by COVID–19 in patients cannot be ignored. In this study, we found that 4 (10.8%) patients experienced severe anxiety and depression, and needed psychological intervention to reduce the psychological trauma. At the same time, the patient's infection parameters needed to be

closely monitored. COVID–19 like other viral types of pneumonia may present as a viral or bacterial infection at an early stage[23–25]. A total of 5 patients with positive pharyngeal swabs for morethan15daysandadecreasedlymphcountreceivedintravenous immunoglobulin, and their lymphocyte count was reported to have improved significantly. Fu Y et al. [26] reported that the use of intravenous immunoglobulin can block FcR activation in the absence of a proven clinical FcR blocker to treat lung inflammationandpreventseverelunginjury.Therefore,theintravenous immunoglobulin used in this study may have some effects in preventing disease progression. However, this requires further studies. By comparing the number of cloudy days of throat swab nucleic acid in patients treated with lopinavir/ritonavir and abidol, it was found lopinavir/ritonavir and abidol may not be effective in treating COVID–19, however, the number of cases in this study was small, and further research using a large sample data should be conducted to determine their effectiveness.

Particular attention to the changes in lactic acid, Fib-C, and D-dimer in patients with COVID–19 should be paid to prevent disease progression. The new coronavirus-specific IgM and IgG antibodies can be used to supplement the nucleic acid detection methods for COVID–19 since they provide rapid results. Besides, there is also a need to pay attention to the problem of nucleic acid positive in stool and take appropriate preventive measures as early as possible. Finally, the use of lopinavir/ritonavir and abidol in COVID–19 patients may not be effective hence more effective treatments should be investigated.

Methods

Study design and participants

This is a single-centered, retrospective study. A total of 37 COVID–19 samples were collected from confirmed patients admitted from January 23 to February 25, 2020, at our hospital, Dazhou Central Hospital, Sichuan Province, China. The hospital admitted a total of 37 COVID–19 patients diagnosed by RT-PCR from the city. The study was approved by the Ethics Committee of Dazhou Central Hospital, and we confirm that all research was performed in accordance with relevant guidelines/regulations. In addition, the written informed consent was obtained from all patients.

Procedures

Patient demographics, clinical, laboratory and other data were collected from the patients' medical records. Their clinical results were followed up until March 18, 2020. All COVID–19 cases were detected from throat swabs, blood, and stool. During hospitalization, the patients got tested for influenza A virus (H1N1, H3N2), influenza B virus, respiratory syncytial virus, adenovirus and new coronavirus pneumonia which are routinely screened in our laboratory. Real-time RT-PCR was used to detect viral nucleic acids from the throat swabs and stool. Also, all the patients underwent a chest CT scan.

Outcomes

We describe the patient's epidemiological data, abnormal biochemical indicators, the rarely counted pharyngeal swab nucleic acid positive durations, stool nucleic acid positive ratios, and specific antibody test results.

Statistical analysis

The mean (SD) was used for normally distributed data, otherwise, the median (IQR) and the categorical variable count (%) were used. Statistical analyses were performed using SPSS (version 19.0) software.

Declarations

Data availability

All materials, data and associated protocols could be available from the corresponding authors by email.

Acknowledgements

This project was funded by the Science and Technology Bureau of Dazhou City, Sichuan Province, China. However, the funding agency did not play any role in designing the study, data collection and analysis, data interpretation and report writing.

Author contributions

CL collected the epidemiological and clinical data and processed statistical data, also responsible for summarising all data related to the patients and drafted the manuscript. FZ, PW, FZ and XZ are responsible for coordinating the work of various departments. CL,FZ, PW, FZ and XZ revised the final manuscript. HW, SD and DL assisted in data analysis. JL and CX assistd in data collection. QG assisted in consulting the literature. FZ is responsible for the source of funds.

Competing interests

The authors declare no competing interests.

References

1. Guan, WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. (2020). Doi: 10.1056/NEJMoa2002032.
2. Chen, NS, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive *Lance*t. **395**, 507-513 (2020).
3. Zhu, N, et al. A Novel Coronavirus from Patients with Pneumonia in China, *N Engl J Med*. **382**,727-733(2020).
4. Liu, Z, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *J Med Virol*. (2020). Doi: 1002/jmv.25726.

5. Xu, J, et al. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*. **12**. (2020). Doi: 10.3390/v12020244.
6. Wang, LF, et al. Review of bats and SARS. *Emerg Infect Dis*. **12**, 1834-1840(2006).
7. Ge, XY, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*. **503**, 535-538(2013).
8. Chen, Y, Guo, D. Molecular mechanisms of coronavirus RNA capping and methylation. *Virol Sin*. **31**, 3-11(2016).
9. Yin, Y, Wunderink, RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* **23**, 130-137(2018).
10. Song, Z, et al. From SARS to MERS, Thrusting Coronaviruses into the *Viruses* **11**. (2019). Doi: 10.3390/v11010059.
11. Wu, YC, Chen, CS, Chan, YJ. The outbreak of COVID-19: An overview. *J Chin Med Assoc*. **83**, 217-220(2020).
12. New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 6). *Tianjin Journal of Traditional Chinese Medicine*. 1-5(2020).
13. Bai, Y, et al. The value of FDP/FIB and D-dimer/FIB ratios in predicting high-risk APL-related thrombosis. *Leuk Res*. **79**, 34-37(2019).
14. Shi, F, Yu, A, Yuan, Clinical Significance of Detection of Coagulation Indexes, Immune Factors and Inflammatory Factors in Patients with Pregnancy-Induced Hypertension Syndrome in China. *Iran J Public Health*. **48**, 681-687(2019).
15. Han, H, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 *Clin Chem Lab Med*. (2020). Doi: 10.1515/cclm-2020-0188.
16. Zhou, F, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort *Lancet*. (2020). Doi: 10.1016/S0140-6736(20)30566-3.
17. Gao, Y, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. *J Med Virol*. (2020). Doi: 1002/jmv.25770.
18. Peng, YD, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi*. **48**, E004 (2020). Doi: 3760/cma.j.cn112148-20200220-00105.
19. Li, Q, et al. The value of SARS-CoV-2 IgM / IgG antibody detection in the diagnosis of new coronavirus pneumonia. *International Journal of Laboratory Medicine*, 1-10(2020).
20. Zhang, J, Wang, S, Xue, Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. *J Med Virol*. (2020). Doi: 10.1002/jmv.25742.
21. Xie, C, et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. *Int J Infect Dis*. (2020). Doi: 10.1016/j.ijid.2020.02.050.
22. Zhang, W, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. **9**, 386-389(2020).

23. Sarda, C, Palma, P, Rello, Severe influenza: overview in critically ill patients. *Curr Opin Crit Care*. **25**,449-457(2019).
24. LeMessurier, KS, et al. Allergic inflammation alters the lung microbiome and hinders synergistic co-infection with H1N1 influenza virus and Streptococcus pneumoniae in C57BL/6 mice. *Sci Rep*. **9**, 19360 (2019). Doi: 10.1038/s41598-019-55712-8.
25. Gu, L, et al. Dynamic Changes in the Microbiome and Mucosal Immune Microenvironment of the Lower Respiratory Tract by Influenza Virus *Front Microbiol*. **10**, 2491(2019). Doi: 10.3389/fmicb.2019.02491.
26. Fu, YJ, Cheng, YX, Wu, Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Virol Sin*. (2020). Doi: 10.1007/s12250-020-00207-4.

Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

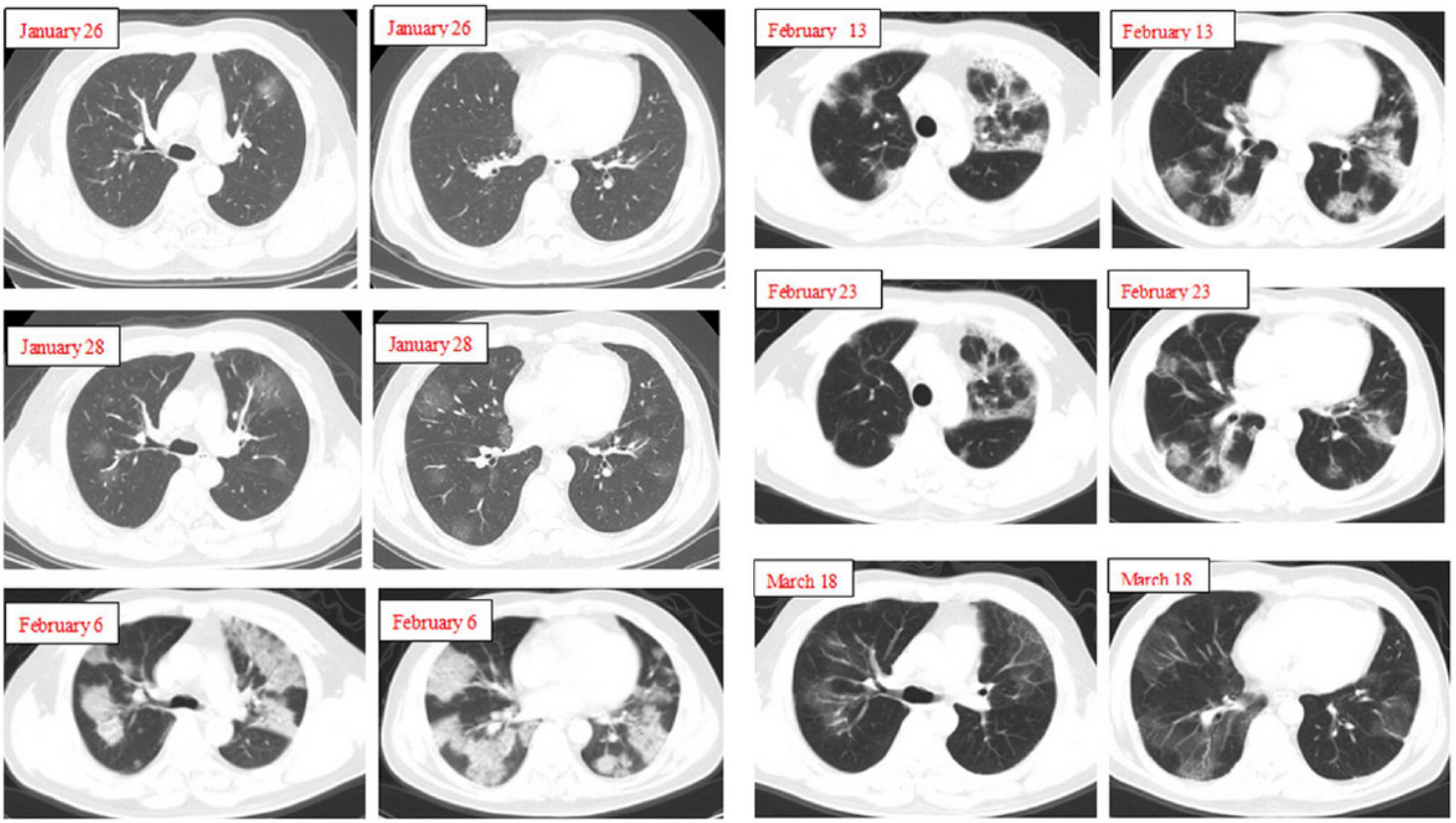

Figure 1

Changes of chest CT in patients with COVID-19.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf