Epidemiology, Clinical Characteristics and Short-term Follow-up of Asymptomatic and Non-severe COVID-19 Patients

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Abstract

COVID-19 broke out in Wuhan in 2019, and spread rapidly around the world. More than 80% of COVID-19 patients are asymptomatic and non-severe, which may be an important source of infection. Therefore, the infectivity, clinical characteristics and outcome of such patients should be studied. The epidemiological data of 108 COVID-19 patients, as well as the clinical characteristics and treatment conditions of 100 asymptomatic and non-severe patients in Bozhou City, Anhui Province were collected. A retrospective analysis of the infectivity of asymptomatic patients was carried out, and a comparative study on clinical characteristics between asymptomatic patients and non-severe patients was also conducted. Eighty-six non-severe patients mainly had a cough (81.4%) and fever (70.9%), and only a few had the symptoms of upper respiratory tract infection such as sore throat (9.3%) and running nose (4.7%). Lymphopenia (20.9%) and elevated C-reaction protein (57.0%) were more frequent in non-severe patients compared with asymptomatic patients which were 0% and 14.3%, respectively. Among 100 asymptomatic and non-severe patients, 84 patients showed abnormal findings on the first chest CT, but meanwhile, 19 patients showed negative results on the viral RNA test. In 14 asymptomatic patients, five had lung abnormalities, which were all pure ground glass opacity. Eleven patients were infected by two asymptomatic patients; in the whole course of the disease, the two patients remained asymptomatic, but chest CT showed multifocal GGO. The time for clearance of SARS-CoV-2 in 12 patients taking methylprednisolone was longer than in other patients (21.2 d vs. 16.4 d). During follow-up, lung lesions found by chest CT in 58.3% of patients completely disappeared. Asymptomatic patients with abnormal chest CT were highly infectious, so SARS-CoV-2 RNA test, combined with a chest CT scan, could discover asymptomatic patients with strong infectivity. The application of glucocorticoids might lengthen the clearance time for SARS-CoV-2 RNA. Both asymptomatic and non-severe COVID-19 patients showed a better prognosis.

Keywords: SARS-CoV-2, asymptomatic infection, non-severe COVID-19 epidemiology, clinical characteristics, chest CT

1. Introduction

Since the outbreak of Coronavirus Disease 2019 (COVID-19) in Wuhan, China at the end of 2019, more than 200 countries, areas or territories have been affected (WHO, 2020). The pathogen of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu N, Zhang D & Wang W, et al., 2020), a new coronavirus, which has only 79.6% homology with the nucleotide of SARS-CoV (Zhou P, Yang XL & Wang XG,

et al., 2020). SARS- CoV-2 mainly infects cells through a combination of S-glycoprotein of virus and human ACE2 receptor; the study on the structure and biophysical properties of S-glycoprotein showed that the affinity of S-glycoprotein to cell ACE2 receptor was 10 to 20 times as high as that of SARS- CoV (Wrapp D, Wang N & Corbett KS, et al., 2020), indicating that SARS-CoV-2 had much higher infectivity than SARS-CoV, which was an important cause for a global pandemic of COVID-19.

In addition to respiratory failure due to lung injury, SARS-CoV-2 can also cause damage to multiple systems, including the digestive system, urinary system, and cardiac system (Wang Z, Yang B, Li Q, Wen L & Zhang R., 2020, Guan WJ, Ni ZY & Hu Y, et al., 2020, Guo YR, Cao QD & Hong ZS, et al., 2020, Huang C, Wang Y & Li X, et al., 2020). Unlike SARS and MERS, COVID-19 had a relatively low mortality rate, but stronger infectivity (Peeri NC, Shrestha N & Rahman MS, et al., 2020), de Wit E, van Doremalen N, Falzarano D & Munster VJ., 2016, Li Q, Guan X & Wu P, et al., 2020), and caused widespread epidemic in a short time. Non-severe COVID-19 patients had relatively mild symptoms, so they might delay in seeking medical care, and become major spreaders of COVID-19. Asymptomatic patients also had infectivity, which made it harder to prevent and control COVID-19 (Wang Y, Liu Y, Liu L, Wang X, Luo N & Ling L., 2020).

Bozhou is an administrative area of Anhui Province, with a population of over 5.39 million. Since the discovery of the first case of COVID-19 on January 21, 2020, 108 patients have been confirmed so far. The viral spreading has been rapidly controlled by various measures, such as chest CT, SARS-CoV-2 RNA screening and hospital isolation for those who have close contact with confirmed cases. We collected the epidemiological and clinical data of asymptomatic and non-severe COVID-19 patients confirmed in Bozhou, and performed a retrospective analysis of their epidemiology, clinical characteristics and outcome.

2. Material and Methods

2.1 Patients

From January 21 to February 12, 2020, 108 COVID-19 patients were discovered in Bozhou, and all were confirmed by real-time quantitative PCR for the detection of SARS-CoV-2. In accordance with the *Guideline for the Diagnosis and Treatment of COVID-19* (the Seventh Trial Version), non-severe COVID-19 patients can be divided based on clinical symptoms and chest CT findings: mild patients: those with mild clinical symptoms and without pneumonia manifestation on chest imaging; ordinary patients: those with fever and respiratory symptoms, as well as pneumonia manifestation on chest imaging, but have no dyspnea or respiratory failure, which appear in severe patients (National Health Commission of the People's Republic of China, 2020). In this study, asymptomatic patients refer to those without symptoms before and after diagnosis and treatment.

This observational study was approved by Institutional Review Committee of Lixin County People's Hospital. Due to the reason that the study was a retrospective observational study, and COVID-19 was listed as an emergency public health event, the Ethics Review Committee waived the requirement for informed consent.

2.2 Date Collection

The 100 SARS-CoV-2-infected patients were all isolated and treated in the same local hospital. We retrospectively collected the clinical charts, nursing records, laboratory examination results, chest CT images, treatment results and outcomes of these patients. The epidemiological data of all the 108 COVID-19 patients in Bozhou were offered by local CDC.

2.3 Discharge and Follow-up

The discharge criteria should follow the *Guideline for the Diagnosis and Treatment of COVID-19* (the Seventh Trial Version) issued by the National Health Commission of the People's Republic of China: (1) Patients with no fever for at least 72 hours; (2) Respiratory symptoms have been significantly improved; (3) There is evidence of improvement in chest CT or X-ray images; (4) There are two consecutive negative results of detection of SARS-CoV-2 RNA, and the RT-PCR interval of SARS-CoV-2 detection is at least 24 hours (National Health Commission of the People's Republic of China, 2020). All patients should be isolated at home after discharge for 14 days and monitored for SARS-CoV-2 RNA and chest CT.

2.4 Statistical Analysis

The continuous variables were expressed as a mean value and a standard deviation or a median value; and classified variables were expressed as counts and percentages. Continuous variables were compared among groups by Kruskal-Wallis test, and classified variables were appropriately compared among groups by Chi-squared test and Fisher exact test. SPSS software version 26.0 was used for statistical analyses, p value less than 0.05 was considered statistically significant.

3. Results

Among the 108 COVID-19 patients, there were three (2.8%) severe patients, 91 (84.3%) non-severe patients, and 14 (13.0%) asymptomatic patients. Three severe patients and five non- severe patients were transferred to other hospitals. We performed a retrospective analysis on the clinical and epidemiological characteristics of the 100 COVID-19 patients isolated and treated in local hospitals, involving 14 asymptomatic patients and 86 non-severe patients. The basic data of patients in these two groups were shown in Table 1. There was no difference in gender between the two groups of patients, but there were more children in the group of asymptomatic patients (35.7% vs 5.8%). Among the non-severe patients, eight (9.3%) had complications, mainly the diabetes (4.7%) and obesity (4.7%), while asymptomatic patients had no complications.

Clinical characteristics of these patients were shown in Table 2. The most common symptom was cough (81.4%), followed by fever (70.9%), and there were rare upper respiratory symptoms, such as sore throat and running nose, which accounted for 9.3% and 4.7%, respectively. Compared with asymptomatic patients, non-severe patients were more significant in the reduction of lymphocytes (p = 0.068), and elevated C-reactive protein (CRP) (p = 0.004).

All patients underwent chest CT scan and SARS-CoV-2 detection. 84 patients (including five asymptomatic patients) had abnormal shadows in their lungs, however, among whom, at the same time of the first CT scan, 19 patients had negative results of SARS-Cov-2 RNA detection. 16 patients had no lung lesions in the whole course of the disease, and each of the 16 patients was given four chest CT scans on average (two to seven scans). The lesions were mainly distributed in multiple lobes (78.6%) and the periphery of the lung (65.5%). The main lesions were pure ground glass opacity (GGO, 67.8%), mixed pattern (mixed with consolidation and GGO, 66.7%), vascular enlargement (11.9%), reticular intralobular line thickening (9.5%), and air bronchogram (8.3%), see Figure 1. Lesions found by chest CT scans of five asymptomatic patients were all pure GGO.

A total of 11 COVID-19 patients were infected by two asymptomatic patients. Case 33 returned to Bozhou from Wuhan on January 14, and stayed with his wife, who first had chest tightness; thereafter both of them were confirmed of COVID-19 through chest CT and SARS- CoV-2 RNA detection. Later, their family members were successively confirmed, and all had a fever and dry cough. Case 33 attended a wedding on January 20, and Case 40 and Case 22 were thereby infected by Case 33. Case 8 shared a public bathroom with Case 33, had a fever 10 days later, and was confirmed of infection through chest CT and SARS-CoV-2 RNA detection. Five patients (case 25, 12, 45, 36, 34) were negative in the initial SARS-CoV-2 RNA detection, but chest CT showed abnormalities, as shown in Figure 2A.

Case 54 returned to Bozhou from Wuhan on January 17, and stayed with his parents. On January 28, his father had fever, and then confirmed COVID-19 through chest CT and SARS-CoV-2 RNA detection on January 29. His mother had a cough on January 26, and virus RNA detection showed a negative result on February 5, but chest CT indicated abnormalities.

On February 7, virus RNA detection showed a positive result. Case 54 was confirmed on January 31, but had no symptoms in the course of the disease, as shown in Figure 2B.

All patients met the discharge criteria (National Health Commission of the People's Republic of China, 2020). The average time for non-severe patients to meet the discharge criteria was 17.7 ± 6.7 days, which was shorter in asymptomatic patients (12.8 ± 6.3 days) (p = 0.015). All patients were treated with Arbidol and traditional Chinese medicine, whereas 12 patients were treated with methylprednisolone for three days (40 mg/d). As for these patients treated with methylprednisolone, the time for clearance of SARS-CoV-2 was $21.2 \pm (\text{days})$, which was significantly longer than that for patients without hormonal therapy ($16.4 \pm 6.9 \text{ days}$) (p = 0.014). All patients were isolated at home after discharge, with the median follow-up time of 51 (36 - 69) days. During the follow-up, SARS-CoV-2 RNA detection turned positive again in five patients. At that time, they were asymptomatic, CT showed no new lesions in the lungs, and no others were infected by them.

The median follow-up time of chest CT after discharge was 31 (9 - 43) days, and the results showed that lung lesions in 58.3% of patients completely disappeared, Figure. 3. In 27.4% of patients, most of the lesions in the lung were absorbed and only remained pure GGO; 14.3% of patients had residual GGO with intralobular line thickening and some stripe-like opacity. These changes could also be observed in the process of lung lesions improvement in patients with complete absorption of lesions. Among the 14 asymptomatic patients, five had lung abnormalities, and there was no difference in imaging characteristics from other patients, but all showing pure GGO with a small range of lesions and significantly improved in a short period of time.

4. Discussion

COVID-19, which broke out in Wuhan in 2019, rapidly spread globally. Being different from SARS and MERS, COVID-19 led to a smaller proportion of severe patients, but higher infectivity (Munster VJ, Koopmans M, van Doremalen N, van Riel D & de Wit E., 2020, Li Q, Guan X & Wu P, et al., 2020, Chen J., 2020). A study carried out by Chinese Centre for Disease Control and Prevention on 44672 COVID-19 patients diagnosed in China showed that non-severe patients accounted for 80.9%, and asymptomatic patients accounted for 1.2% (Weekly CC, 2020). From January 2020, 108 COVID- 19 patients were confirmed in Bozhou, including 84.3% of non-severe patients, which were similar to the results of other studies (Weekly CC, 2020, Guan WJ, Liang WH & Zhao Y, et al., 2020, Tian S, Hu N & Lou J, et al., 2020). Asymptomatic patients accounted for 13.0%, which was significantly higher than the national level (Tian S, Hu N & Lou J, et al., 2020). Asymptomatic patients should be diagnosed by SARS-CoV-2 RNA screening and antibody screening. All asymptomatic patients in Bozhou have been diagnosed through chest CT and S ARS-CoV-2 RNA detection. In some patients, CT abnormalities appeared earlier than the positive result of SARS-CoV-2 RNA detection. Although the proportion of asymptomatic patients in Bozhou was higher than the national level, some asymptomatic patients might still be undetected. Nishiura H et al. estimated that the proportion of asymptomatic patients would be 30.8% (Nishiura H, Kobayashi T & Suzuki A, et al., 2020). The relatively high proportion of mild patients and asymptomatic patients, as well as the high affinity of the virus to receptors might be the key factors leading to the wide spread of COVID-19.

This study showed that the number of children was higher among asymptomatic patients, who accounted for 35.7%. In our study, asymptomatic patients had no complications, and non-severe patients only had a small number of complications, mainly diabetes (4.7%) and obesity (4.7%). A meta-analysis showed that the main complications of COVID-19 patients were hypertension (16.37%), cardiovascular disease (12.11%), and diabetes (7.63%), which were associated with poor prognosis (Guan WJ, Liang WH & Zhao Y, et al., 2020, Emami A, Javanmardi F, Pirbonyeh N & Akbari A., 2020). A high proportion of children and fewer complications may be the characteristics of asymptomatic and non-severe COVID-19 patients. C-reaction protein always significantly increased in COVID-19 patients, which was associated with the severity of COVID-19 and the range of pulmonary lesions (Chen N, Zhou M & Dong X, et al., 2020, Wang L., 2020). It was found that asymptomatic patients had fewer CRP abnormalities than non-severe patients.

The chest CT imaging changes were consistent with the results reported previously (Wang Y, Dong C & Hu Y, et al., 2020), featured in multilobar, multifocal, and peripheral lesions of the lung. The images mainly showed pure GGO, ground glass opacity mixed with consolidation, vascular enlargement and reticular intralobular line thickening. During follow-up, lung opacity completely disappeared in 58.3% of patients. Being different from pulmonary fibrosis and abnormal lung function associated with SARS (Xie L, Liu Y & Xiao Y, et al., 2005), SARS-CoV-2 had less effect on lung functions in asymptomatic and non-severe patients.

The infectious studies on asymptomatic patients were mainly limited to those with a small sample size. The chest CT often showed abnormalities, and some patients had typical symptoms after diagnosis (Hu Z, Song C & Xu C, et al., 2020), who were obviously infectious. In this study, we defined asymptomatic patients as asymptomatic throughout the course of the disease. Among 14 asymptomatic patients, two patients with abnormal chest CT displayed highly infectivity. We speculated that the asymptomatic patients with lung abnormalities would have stronger infectivity than those without lung abnormalities. Therefore, chest CT could be performed to predict the infectivity of asymptomatic patients, who would therefore be isolated and treated in different manners. In some patients, chest CT abnormalities appeared earlier than the positive results of SARS-CoV- 2 RNA detection, which, combined with CT scanning, could be used to discover asymptomatic patients as early as possible among high-risk patients (Xie X, Zhong Z, Zhao W, Zheng C, Wang F & Liu J., 2020). Agostini *et al.* showed that low-dose CT could effectively detect lung abnormalities in COVID-19 patients, and its radiation dose was much lower than the third-generation conventional CT scan (Agostini A, Floridi C & Borgheresi A, et al., 2020). Therefore, low-dose CT can be adopted as an acceptable option during COVID-19 screening, especially for children patients.

In this study, all patients were cured and discharged, suggesting favorable prognosis for asymptomatic and non-severe patients. All patients were treated with traditional Chinese medicine and Arbidol during hospitalization. A limited number of studies showed that Arbidol could play a certain antiviral role (Deng L, Li C & Zeng Q, et al., 2020); traditional Chinese medicine had a certain effect on alleviating the symptoms of patients, but its antiviral activity should be further studied (Zhang K., 2020). There were no clinical trials that could determine whether the application of glucocorticoids could improve the prognosis of patients (Zhao JP, Hu Y & Du RH, et al., 2020). Twelve patients in the study received short-term methylprednisolone treatment, and the

virus clearance time of these patients was longer than that of other patients. SARS-CoV-2 RNA test turned positive again in five patients during follow-up, but there were neither symptoms and CT abnormalities, nor evidence of human-to-human transmission. The clinical significance of this phenomenon should be further studied.

5. Conclusions

In the group of asymptomatic patients, there are more children patients; compared with non-severe patients, lymphopenia and elevated CRP are less common. Asymptomatic patients with lung abnormalities are highly infectious, and such patients can be screened through chest CT scan and SARS-CoV-2 RNA detection at an early stage. As for asymptomatic and non-severe patients, the majority of the lung lesions can be completely absorbed, and it is speculated that they will not affect lung functions. Limited data have shown that methylprednisolone could delay the time for eliminating the SARS-CoV-2, therefore, it should be used carefully in these patients. The clinical significance of the phenomenon that SARS-CoV-2 RNA turns positive again in discharged patients is yet unclear, and is therefore to be further studied.

6. Abbreviations

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	syndrome coronavirus 2
CRP	C-reactive protein

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Appendix A

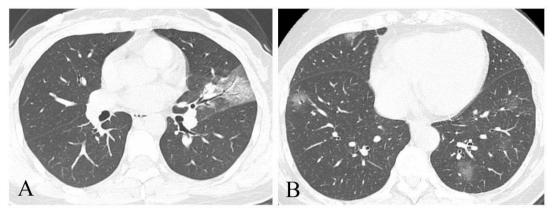


Figure 1. A. Image of a 40-year-old female patient on Day 2 after onset. The image showed GGO, consolidation, intralobular septal thickening (crazy-paving pattern) and air bronchogram. B. Image of a 51-year-old female patient on Day 2 after onset. The chest CT showed multiple pure GGOs around the lungs.

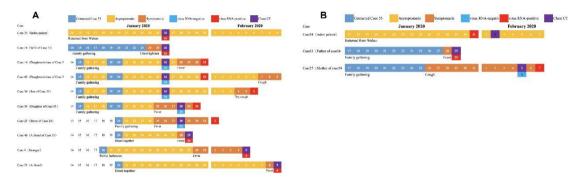


Figure 2. A. Timeline of exposure to index patient case 33 with COVID-19. B. Timeline of exposure to index patient case 54 with COVID-19

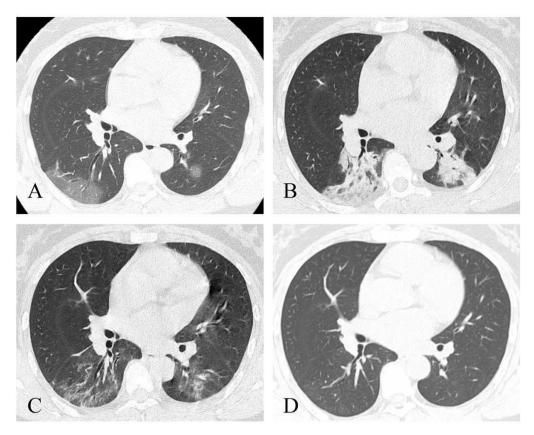


Figure 3. Serial chest CT of a 42-year-old female COVID-19 patient

A. The chest CT on Day 3 after onset showed multiple pure ground glass opacity in both lungs, which were mainly distributed around the lungs. In GGO, vascular enlargement could be observed. B. Chest CT of patient on Day 9 showed that the range of lesions was enlarged and consolidation appeared. C. Chest CT of patients on Day 16 showed the range of lesions shrank, and the majority of the consolidated opacity disappeared. Intralobular line interlobar septa and pleural thickening could be observed. D. Chest CT of patient on Day 41 showed the lesions completely disappeared.

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