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Comparison of clinical and epidemiological characteristics of asymptomatic and symptomatic SARS-CoV-2 infection: A multi-center study in Sichuan Province, China

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ABSTRACT

Objectives: Asymptomatic infection of SARS-CoV-2 has become a concern worldwide. This study aims to compare the epidemiology and the clinical characteristics of SARS-CoV-2 infection in asymptomatic and symptomatic individuals.

Methods: A total of 511 confirmed SARS-CoV-2 infection cases, including 100 asymptomatic (by the time of the pathogenic tests) and 411 symptomatic individuals were consecutively enrolled from January 25 to February 20, 2020 from hospitals in 21 cities and 47 counties or districts in Sichuan Province. Epidemiological and clinical characteristics were compared.

Results: Compared to the symptomatic patients, the asymptomatic cases were younger ($P < 0.001$), had similar co-morbidity percentages ($P = 0.609$), and came from higher altitude areas with lower population mobility ($P < 0.001$) with better defined epidemiological history ($P < 0.001$). 27.4% of well-documented asymptomatic cases developed delayed symptoms after the pathogenic diagnosis. 60% of asymptomatic cases demonstrated findings of pneumonia on the initial chest CT, including well-recognized features of coronavirus disease-19. None of the asymptomatic individuals died. Two elderly individuals with initially asymptomatic infection developed severe symptoms during hospitalization. One case of possible virus transmission by a patient during the incubation period was highly suspected.

Conclusions: The epidemiological and clinical findings highlight the significance of asymptomatic infection with SARS-CoV-2. Inspecting the epidemiological history would facilitate the identification of asymptomatic cases. Evidence supports the chest CT scans for confirmed asymptomatic cases to evaluate the extent of lung involvement.

1. Introduction

Since the outbreak of the coronavirus disease-19 (COVID-19), it has spread rapidly across many provinces in China and many other countries around the world, including South Korea, Japan, Iran, Italy, the United States, Australia, etc. As of late May 2020, over 80,000 cases have been confirmed in China, and more than 5,000,000 cases have now been reported to WHO from 216 countries, areas, or territories [1]. At present, it is considered that the main infection source is through patients with SARS-CoV-2 infection [2]. However, unlike in the case of SARS, people with asymptomatic infection of SARS-CoV-2 are likely source of infection and plays a nonnegligible role in the spread of the epidemic, as supported by multiple previous reports [3–7]. Asymptomatic infection of SARS-CoV-2 has become a serious concern worldwide, as recent research indicated that covert (asymptomatic) cases could represent 60% of all infections and could be seeding new outbreaks [8].

The increase of new cases of COVID-19 in China has decelerated

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease-19; CT, computerized tomography; SD, standard deviation

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significantly recently, however, concerns have been raised regarding the management of asymptomatic individuals, who are difficult to be effectively identified and therefore pose considerable challenges in the containment of the disease and prevention of new outbreaks [9,10]. Some individuals who are asymptomatic in the incubation period could convert to clinically diagnosed COVID-19 cases later, for whom the early detection and corresponding medical support would be beneficial [11]. Therefore, the management of asymptomatic infection is of great significance both in the control of the epidemic and the clinical treatment of infected individuals. However, the epidemiological and clinical characteristics of asymptomatic infection of SARS-CoV-2 have not been fully studied and rarely been compared with the symptomatic infection.

This study aims to fill the gap by comparing the epidemiology and clinical characteristics of asymptomatic and symptomatic individuals with SARS-CoV-2 infection using multi-center data collected in Sichuan province, where the total number of confirmed cases of COVID-19 was 11th highest among 34 provinces and municipalities in China by the beginning of April. We believe the findings may provide further evidence and perspective to the management of asymptomatic infection with SARS-CoV-2.

2. Methods

2.1. Patients

The local ethics committee approval was obtained, and written informed consent was waived for this retrospective study that involved no potential risk to patients.

Consecutive patients between January 25 and February 20,2020 with confirmed SARS-CoV-2 infections by pathogenic evidence were enrolled from hospitals scattered in 21 cities and 47 counties or districts in Sichuan Province, China. The hospitals included tertiary hospitals in urban areas like the city of Chengdu, and county-level hospitals, including in minority areas with high altitude locations. The clinical outcomes were monitored up to March 18, 2020 as the final date of follow-up. Patients with substantial missing medical data or no chest CT examinations were excluded. Data including epidemiological history, demographic characteristics, clinical symptoms, underlying comorbidities, laboratory results, chest CT findings and prognosis were collected from patients' medical records. Included patients were divided into asymptomatic infection group and symptomatic infection group according to the primary reason of the first medical visit.

2.2. Definition of relevant symptoms

Recent (within 1 month) persistent respiratory symptoms (cough, pharyngalgia, rhinorrhoea, shortness of breath, etc.), systemic symptoms (fever, chills, fatigue, muscle aches, headaches, etc.), circulatory symptoms (chest pain, chest distress, palpitation, etc.) and digestive symptoms (diarrhea, vomiting, anorexia, etc.) that were evaluated by physicians and noted in the medical records were considered as suspected relevant symptoms of COVID-19. Long-term chronic diseases, sudden cardio-cerebrovascular accidents, acute abdomen, or trauma were not considered as relevant symptoms, but as comorbidities or concomitant diseases. Asymptomatic cases were defined as showing no above-mentioned relevant symptoms at the time of pathogenic test.

2.3. Strategy for pathogenic diagnosis

In this study, the diagnosis of SARS-CoV-2 infection was based on pathogenic evidence. Two methods were employed: real-time fluorescent PCR to detect nucleic acids of the novel coronavirus, or viral gene sequencing to detect highly homologous genes with known novel coronaviruses (mainly the former). Samples were obtained by swabbing the oropharyngeal or nasopharyngeal mucosa for all asymptomatic individuals and the majority of symptomatic individuals, and bronchoalveolar lavage fluid, sputum, anal swabs or feces for a few symptomatic individuals. According to the specific circumstances of the patient, two or more sampling methods were used to confirm the diagnosis if necessary. Some patients had multiple samples taken. Sampling locations included quarantine areas in hospitals, designated medical observation quarantine areas and home quarantine areas.

2.4. CT image acquisition

All images were obtained on spiral CT equipment with 16 rows or higher and reconstructed as 1 mm–2.5 mm thick sections to ensure optimum image quality for diagnosis. The equipment conformed to the national standard for medical devices. All CT scans were performed within 24 h of pathogenic diagnosis of SARS-CoV-2 infection. Because some of the asymptomatic individuals developed late symptoms after pathogenic diagnosis, it is noteworthy that all CT scans for the asymptomatic individuals were performed during the asymptomatic phase.

2.5. Classification of places of origin and epidemiological history

Patients were classified according to their region of residence as high-altitude areas (plateau section, altitude > 3000 m, with more minority communities and lower population mobility), and regular areas (other parts of Sichuan province, mostly have altitude of 500–2000 m). It is worth mentioning that due to lesser mobility of people from high-altitude areas, the local public health management involved stronger implementation of population screening by obtaining samples from individual homes for pathogenic evaluation. The major sources of the asymptomatic cases collected in this study included: 1). population-based pathogenic screening in outbreak areas with lower mobility and with feasibility of screening from individual homes; 2). Examining the close contacts of confirmed cases in all areas.

Epidemiological history was classified as: indeterminate/no identifiable history; or as:

Type 1: History of travel or residence in the outbreak area (Hubei province, or other communities with confirmed case reports) within 14 days before the disease onset/pathogenic test.

Type 2: Contact history with suspected patients (having fever or respiratory symptoms) in the outbreak area within 14 days before the disease onset.

Type 3: Contact history with COVID-19 patients (nucleic acid test confirmed positive) within 14 days before the onset of the disease.

Type 4: Aggregation: within 14 days before the disease onset. At least one confirmed case detected in an enclosed environment (such as a family house, a construction site, an office, etc.), with one or more cases found with fever or respiratory symptoms at the same time, revealing potential interpersonal transmission or joint exposure of the disease [2].

In order to screen epidemiological histories more thoroughly, travelers were screened routinely by several ways, including self-reporting of travel histories, door-to-door survey of the community, and spot survey at the vital communication lines (including entrances to the cities through the highway). The incubation period of the symptomatic patients was defined as the period between the first exposure date of novel coronal virus to the first onset date of relevant symptoms. If the exposure lasted for a period, the median date of this period was used. If the exposure date was unknown, the case was not included in the statistic calculation of incubation period to avoid substantial bias.

2.6. Statistical analysis

Continuous variables were summarized using the mean ± standard deviation, and categorical variables were presented as counts or percentages. Comparisons between groups was conducted using Chi-Square test for categorical data and Mann-Whitney *U* test for

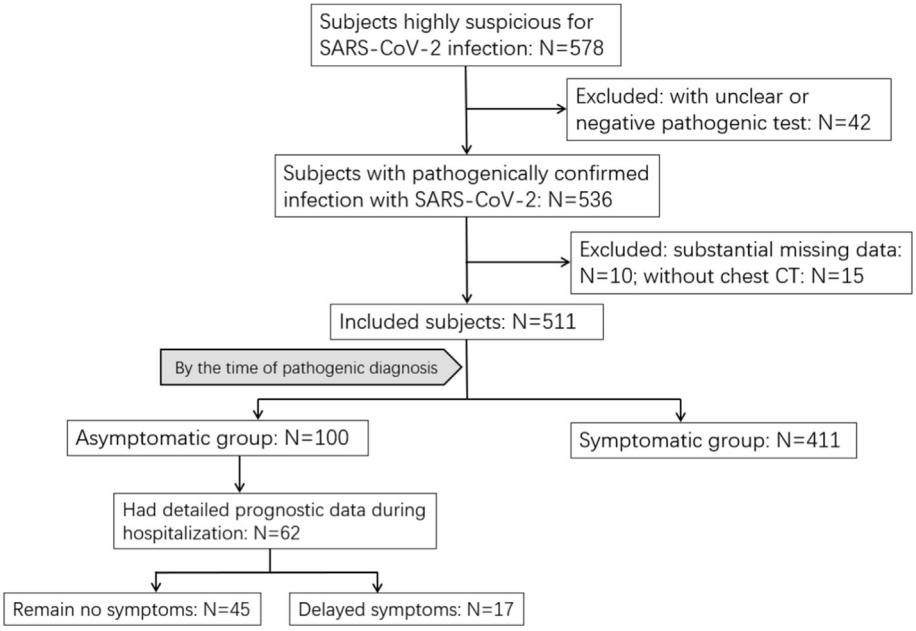

Fig. 1. Flow diagram of subject inclusion.

continuous data. The following parameters were compared between the asymptomatic and symptomatic infection groups:

1. Demographic and clinical characteristics.
2. Epidemiological history and sampling location.
3. Chest CT findings.

$P < 0.05$ was regarded as significant, and all p-values were two-sided. SPSS (Statistics Version 22) was used for data analysis.

3. Results

3.1. Demographic characteristics and symptom distribution

A total of 511 subjects (age range: 1 month to 87 years old) with pathogenically confirmed SARS-CoV-2 infection were included, including 100 individuals in the asymptomatic infection group and 411 patients in the symptomatic infection group. A flow diagram of the subject inclusion process was shown in Fig. 1.

The median incubation period of the symptomatic patients was 6 days (range: 2–15 days). In the asymptomatic group, among 62 subjects who had detailed prognostic data during hospitalization, 17 of them (27.4%) developed relevant symptoms days (median: 7 days, range: 1–13 days) after the pathogenic diagnosis of SARS-CoV-2 infection, including respiratory and systemic symptoms. All these presymptomatic cases showed positive CT findings of pneumonia at admission.

The distribution of symptoms of the symptomatic group is shown in Table 1. 28.9% of the patients had respiratory symptoms only while 32.3% of the patients had systemic symptoms only. A third of patients (33.1%) had symptoms related to multisystem involvement.

The demographic characteristics of all patients are listed in Table 2. The asymptomatic group consisted of predominantly younger individuals including children ($P < 0.001$). No difference was detected in the gender distribution ($P = 0.998$), presence or absence of comorbidities between the two groups ($P = 0.609$).

3.2. Epidemiological history and places of origin

The symptomatic group had significantly more cases with indeterminate epidemiological history (75.2% vs. 5.0% for symptomatic and asymptomatic group, respectively). The asymptomatic group had more cases with type 1 (travel or residence in the outbreak area) and type 3 (contacts with confirmed COVID-19 patients) histories. No type 4 history was identified in this patient cohort.

More asymptomatic cases were from high altitude areas with lower mobility ($P < 0.001$), and had sampling locations outside of hospitals ($P < 0.001$). Fifty-two asymptomatic cases were identified by screening and sampling from individual homes in outbreak areas with lower population mobility, 8 cases were identified by screening among people with travel history to Hubei province, and 34 cases were

Table 1
The distribution of symptoms in the symptomatic CODIV-19 group.

System	Manifestation	Number of cases	Percentage (%)
Respiratory symptoms	Cough (mostly with no sputum)	102	24.8
	Pharyngalgia or runny nose	17	4.1
Systemic symptoms	Fever	98	23.8
	Chills or fatigue	3	0.7
	Muscle aches or headaches	32	7.8
Circulatory symptoms	Chest pain, chest distress or palpitation	10	2.4
Digestive symptoms	Diarrhea, vomiting or anorexia	13	3.2
Multi-system symptoms	Cough and fever	76	18.5
	Cough and other non-fever symptoms	27	6.6
	Fever and other non-cough symptoms	33	8.0
Total		411	100.0

Table 2
The demographic and clinical characteristics.

	Asymptomatic infection (N = 100)	Symptomatic infection (N = 411)	P value
Age, years, mean ± SD	37.7 ± 19.0	44.0 ± 15.4	< 0.001
Age (years) distribution	0–17:14 (14.0%) 18–65:76 (76.0%) Older than 65: 10 (10.0%)	0–17:15 (3.7%) 18–65:360 (87.6%) Older than 65: 36 (8.8%)	< 0.001
Male (%)	55 (55.0%)	226 (55.0%)	0.998
No-comorbidities	77 (77.0%)	304 (74.0%)	0.609
Top three comorbidities	Hypertension: 9, Gastroenteritis: 4, Pulmonary tuberculosis:3	Hypertension:29, Diabetes:26, Hepatitis B: 6, Hyperlipidemia: 6	/
No determinate epidemiological history	5 (5.0%)	309 (75.2%)	< 0.001
Epidemiological history	Type 1: 60 (63.2%) Type 2: 1 (1.0%) Type 3: 34 (35.8%) Type 4: 0	Type 1: 64 (62.7%) Type 2: 6 (5.9%) Type 3: 32 (31.4%) Type 4: 0	/
Regions of origin	High attitude and lesser mobility areas: 66 (66.0%) Regular areas: 34 (34.0%)	High attitude and lesser mobility areas: 37 (9.0%) Regular areas: 374 (91.0%)	< 0.001
Sampling locations	Hospitals: 20 (20.0%) Designated quarantine areas: 41 (41.0%) Home quarantine areas: 38 (38.0%)	Hospitals: 398 (96.8%) Designated quarantine areas: 8 (1.9%) Home quarantine areas: 3 (1.2%)	< 0.001
Positive findings for pneumonia on chest CT	60 (60.0%)	375 (91.2%)	< 0.001
Both lung involvement on chest CT	31 (51.7%)	281 (74.9%)	< 0.001
Prognosis (till March 1st)	Discharge: 48 (48.0%) Death: 0 In treatment and monitoring: 52	Discharge: 298 (72.5%) Death: 2 In treatment and monitoring: 111	/

SD: standard deviation.

identified by examining all traceable close contacts of confirmed infected cases.

The peak time of the disease onset was slightly different in the two groups. The asymptomatic group had two small peaks in early and mid-February 2020, respectively. Whereas the symptomatic group had a wider and higher peak around late January 2020 (Fig. 2).

Following is a noteworthy case of a 19 years old female who returned to her parents' home in Chengdu from a school in Wuhan, the city where the infected cases were firstly and mostly reported. One day after her return, her father, who had otherwise no specific epidemiological history, developed cough and was confirmed to have SARS-CoV-2 infection. Two days later she herself developed cough and fever. Her chest CT showed pneumonia (multiple ground glass opacities in the right lower lung). Two consecutive nucleic acid tests were positive for SARS-CoV-2. Since her symptom onset was later than her father, it is highly suspicious that she transmitted the virus to her father during her incubation period.

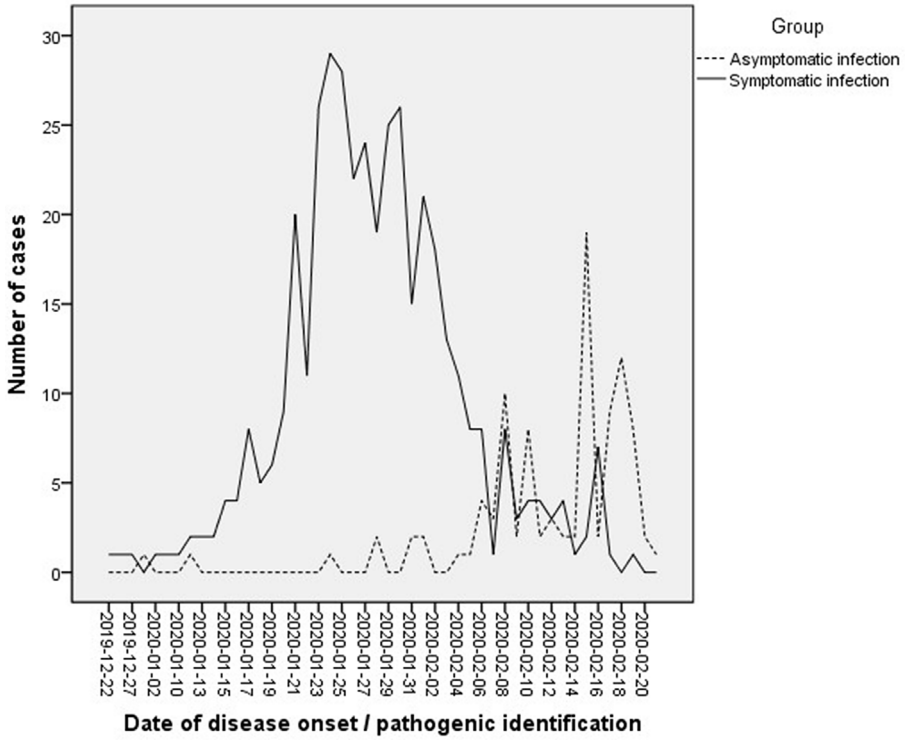

Fig. 2. The plot of time versus number of cases in two groups.

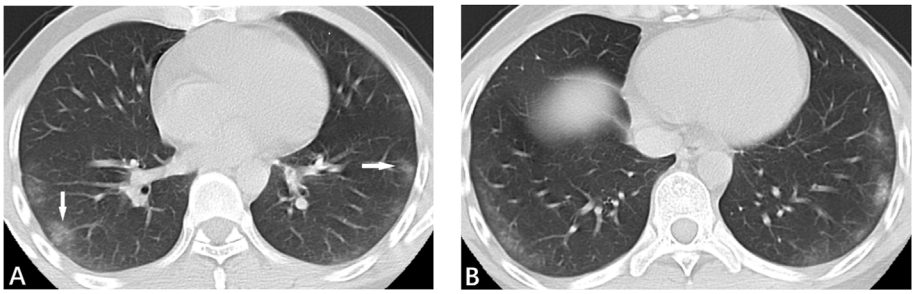

Fig. 3. A case from asymptomatic group. A 35 years old male who lived in an infected area where COVID-19 cases had been reported. He was tested positive for COVID-19 by nucleic acid test by throat swab sampling from home. The patient showed no recent symptoms. Chest CT showed bilateral and peripherally distributed ground glass opacities.

3.3. Imaging features of patients infected with SARS-CoV-2

Remarkably, 60.0% of asymptomatic cases demonstrated positive findings of pneumonia on the initial chest CT (although less than the symptomatic group), and approximately half of them showed bilateral lung involvement. Imaging manifestations ranged from non-specific pulmonary infiltration to well recognized imaging features of COVID-19 including bilateral and peripheral ground-glass opacities and consolidations. Among the 60 asymptomatic cases who demonstrated positive CT findings, 37 cases showed typical multiple peripheral patchy ground glass opacities, some of who showed parenchymal consolidation, interlobular septal thickening, bronchial wall thickening and halo signs or reverse-halo signs. Eighteen cases showed single or several scattered ground glass opacities. 5 cases showed nodular ground glass opacities. Pleural effusion or/and pleural thickening were uncommon. Representative cases from each group are illustrated in Figs. 3 and 4.

3.4. Treatment and prognosis

According to the diagnosis and treatment scheme issued by the China Health Committee, different treatment regimen were administered according to the severity of the disease [2]. All patients in the symptomatic group received antiviral therapy; mostly α-interferon aerosol inhalation combined with lopinavir/ritonavir tablets. Oxygen therapies were given according to the patient's oxygen saturation. Supportive treatments included expectorant, cough drops, antiasthma agents were given according to the symptoms and co-morbidities were treated. Antibiotics were given when there was evidence of bacterial infection. Respiratory and circulatory support was provided to patients of severe and critically types. Glucocorticoids (such as methylprednisolone) were used for short term.

Asymptomatic cases were given antiviral therapy if the CT imaging showed positive findings for pneumonia. Co-morbidities were treated. Those who had negative CT results and no co-morbidities were closely observed. Two cases in the asymptomatic group became severe type during the clinical course, including one elder female (83 years old) who was given methylprednisolone because of low oxygen saturation, and one elder male (84 years old) with comorbidity of brain infarction and pulmonary emphysema.

Up to March 18, 3 patients (0.7% in the group) died in the symptomatic group while there were no deaths in the asymptomatic group. All other patients were discharged from the hospital. Discharge standards were: body temperature recorded as normal for more than 3 days, relevant symptoms improved significantly, and nucleic acid tests were negative for two consecutive times (sampling interval was at least 1 day) [2].

4. Discussion

In this multi-center retrospective study, we identified a relatively large number of asymptomatic cases with confirmed SARS-CoV-2 infection by pathogenic evidence. In comparison to the symptomatic patients, asymptomatic cases were significantly younger, had similar co-morbidity percentages, were more likely from high altitude and

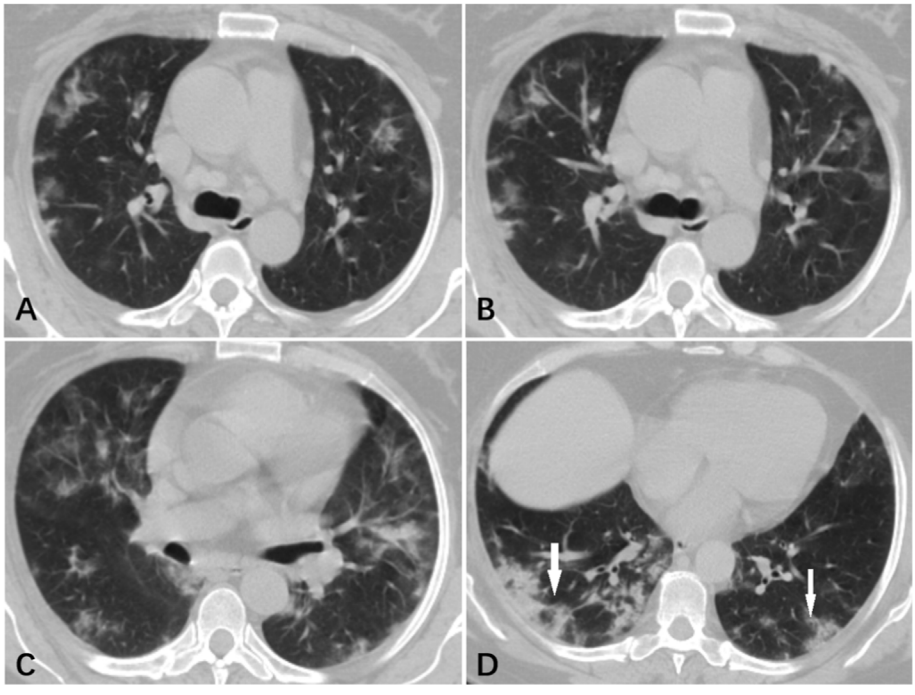

Fig. 4. A case from asymptomatic group. A 53 years old female who lived at an infected area where COVID-19 cases had been reported. She tested positive for COVID-19 by nucleic acid test but showed no symptoms at the time of the CT scan, and had abdominal discomfort 10 days after the scan. Chest CT showed bilateral, multiple ground glass and consolidative pulmonary opacities.

lower mobility areas with better defined epidemiological history. Remarkably, 60.0% of asymptomatic cases demonstrated findings of pneumonia on chest CT, including some typical imaging features of COVID-19. More than a quarter (27.4%) of well-documented cases who had been asymptomatic by the time of pathogenic diagnosis developed delayed symptoms and turned out to be presymptomatic. Two elderly individuals with initially asymptomatic infection developed severe clinical symptoms during hospitalization. At least one case of possible virus transmission by a patient during the incubation period was highly suspected.

All these findings suggest the relevance and significance of asymptomatic infection of SARS-CoV-2 in terms of both epidemiological and clinical management. The asymptomatic cases may still have considerable clinical risks because of similar proportion of co-morbidities (which was believed to be associated with disease risk [12,13]) even with younger age, possible delayed symptoms, and a high rate of positive imaging findings on chest CT. Some of the results were broadly consistent with another study with a smaller sample size of asymptomatic cases (N = 24), which reported 20.8% of cases with delayed symptoms and 70% cases with positive CT findings [14]. Individuals with asymptomatic infection of SARS-CoV-2 also carry public health risks because they are likely contagious, as reported by previous studies and one case in this study [9,15]. Specifically, the infectivity of asymptomatic cases would bring more attention to the medical protection of the medical staff, who have frequent close contacts with accompanying family members of the symptomatic patients [16,17].

The asymptomatic group of SARS-CoV-2 infection was often overlooked or underestimated in previous trials and investigations. Previous studies reported 13, 15, and 24 asymptomatic cases based on the experience in Beijing, Wuhan, and Nanjing, respectively [14,18,19]. These cases were found incidentally or by screening the close contacts of confirmed cases. Another study based on the practice in a Fangcang Hospital that included 1012 individuals reported 30 asymptomatic cases [20]. To our best knowledge, this study reports the largest number of asymptomatic cases of SARS-CoV-2 so far (N = 100), providing a unique opportunity to investigate this group and compare it with the symptomatic group more reliably.

In this study, more asymptomatic cases were from high altitude areas where the population movement was relatively less, the epidemiological histories of people were clearer, and the local public health management involved stronger implementation of population screening by sampling from individual homes for pathogenic testing after the disease outbreak. This could partially explain why considerable numbers of asymptomatic cases were identified. This may also be related to different genetic susceptibility or racial differences in the population from high altitude and regular altitude areas, however, currently there is lack of sufficient evidence to support this. It is still believed that the population is generally susceptible to the virus [21]. Although some controversy remains whether to implement population screening, the scientific and evidence-based discussion should be warranted.

The curves of case numbers over time indicated later, smaller, and more concentrated time peaks for the asymptomatic group. Possible explanation might be the lack of awareness of asymptomatic infection by late January. As public concerns regarding possible transmission by asymptomatic individuals were then raised, administrators of the 21 cities and 47 counties/districts adopted intensive screening successively in a relatively short period. This indicated that the identification of asymptomatic cases might still partly depend on the intensity of screening.

This study has some limitations. First, a large-scale and fully inclusive population screening by pathogenic tests for asymptomatic cases was not feasible socially or economically, especially when the knowledge of the disease was still accumulating and evolving in February. Nevertheless, considerable efforts have been made in outbreak regions with lower population mobility and with feasibility of screening, and substantial number of asymptomatic cases were identified despite some overall selection bias. Second, there are inevitably many challenges related to data collection when conducting a broad and extensive investigation. In the asymptomatic group, only 62 patients who had detailed prognostic data during hospitalization were investigated for delayed symptoms. This would lead to an underestimation of cases with delayed symptom onset. In addition, in a large proportion of symptomatic patients, including 75.2% who had unknown epidemic history, it was not possible to calculate the incubation period. Third, laboratory results were not systematically collected and analyzed due to the different protocols, equipment and diagnostic standards across the hospitals from 21 cities and 47 counties or districts. Finally, most of the treatment courses of included patients were descriptive and did not allow detailed calculation and statistical comparison.

In conclusion, asymptomatic cases of SARS-CoV-2 infection may have considerable clinical risks because of possible delayed symptoms and a high rate of positive imaging findings on chest CT. They also carry public health risks because of the likelihood to spread infection. The discussion of this under-recognized group is needed in order to treat the disease and control the spread of infection. Evidence supports the chest CT scans for confirmed asymptomatic cases to evaluate the extent of lung involvement.

Author contribution

W Kong, Y Wang, H Pu and Clinical Research Collaborative Group of Sichuan Provincial People's Hospital collected the epidemiological and clinical data, J Hu provided technical support. W Kong processed statistical analysis. Y Wang and W Kong interpreted the results and drafted the manuscript. A Chughtai provided critical revision of the manuscript. H Pu provided administrative support.

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CRediT authorship contribution statement

Weifang Kong: Conceptualization, Methodology, Investigation, Formal analysis. **Yuting Wang:** Conceptualization, Investigation, Validation, Writing - original draft. **Jinliang Hu:** Methodology. **Aamer Chughtai:** Writing - review & editing. **Hong Pu:** Supervision, Project administration.

Declaration of competing interest

The authors declare no conflicts of interest.

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