Characterization of an asymptomatic cohort of SARS-COV-2 infected individuals outside of Wuhan, China

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Brief Summary

Asymptomatic individuals infected with SARS-CoV-2 are an important source of transmission. Early identification of asymptomatic cases with subsequent isolation and treatment may contribute to decreased transmission and mortality.

Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, resulting in the coronavirus disease COVID-19) is highly transmissible among people. Asymptomatic infections are also an important source of infection. Here, we aimed to further clarify the epidemiologic and clinical characteristics of asymptomatic SARS-CoV-2 infections.

METHODS

We identified close contacts of confirmed COVID-19 cases in northeast Chongqing who were RT-PCR+ yet remained asymptomatic throughout their infections. We stratified this cohort by normal versus abnormal findings on chest CT, and compared the strata regarding comorbidities, demographics, laboratory findings, viral transmission and other factors.

RESULTS

Between January and March, 2020, we identified and hospitalized 279 RT-PCR+ contacts of COVID-19 patients. Of these, 63 (23%) remained asymptomatic until discharge; 29 had abnormal and 34 had normal chest CT findings. The mean cohort age was 39.3 years, and 87.3% had no comorbidities. Mean time to diagnosis after close contact with a COVID-19 index patient was 16.0 days (range 1 to 29), and 13.4 days and 18.7 days for those with abnormal and normal CT findings, respectively ($p < 0.05$). Nine subjects (14.3%) transmitted the virus to others; 4 and 5 were in the abnormal and normal CT strata, respectively. The median length of nucleic acid turning negative in asymptomatic COVID-19 patients was 13 days, compared to 10.4 days in those with normal chest CT ($p < 0.05$).

CONCLUSIONS

A portion of these asymptomatic individuals, with and without abnormal chest CT scans, were capable of transmitting the virus to others. Given the frequency and potential infectiousness of asymptomatic infections, testing of traced contacts is essential. Studies of the impact of treatment on asymptomatic RT-PCR+ individuals on disease progression and transmission should be undertaken.

Introduction

In December 2019 a novel coronavirus, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a large outbreak of infectious disease, designated COVID-19. It spread from Wuhan, Hubei province, to the whole of China and continues to pose a great threat to public health[1]. Compared to SARS-CoV or MERS-CoV, it appears to be transmitted more easily[2-4]. SARS-CoV-2 can be transmitted through a variety of modes, including droplets, close contact, aerosol and potentially also fecal-oral transmission[5, 6]. People of all ages are generally susceptible to the virus. Symptomatic COVID-19 patients and asymptomatic cases are both a source of infection and patients in the incubation period can transmit SARS-CoV-2 to other persons [7-10].

Patients with symptoms are more likely to be detected. Among patients with SARS-CoV-2, fever has been the most common symptom, followed by dry cough, dyspnoea, myalgia, headache and diarrhoea[11-13]. In severe COVID-19 cases, symptoms can progress to acute respiratory distress syndrome, septic shock and metabolic acidosis [14]. The clinical presentation of COVID-19 therefore ranges from asymptomatic to severe respiratory illness[15]. The presentation of symptoms provides an opportunity for case detection and isolation, facilitating the interruption of transmission. Because most SARS-CoV patients had severe symptoms, they were relatively simple to identify and isolate, thus interrupting the chain of transmission. Unfortunately, COVID-19 has an incubation period from infection to onset of symptoms that lasts an average of 10 days (with a reported range of 2-14 days)[11,16,17]. The virus is also able to spread from one person to another before any symptom onset[14]. It is reported that about 1.2% of the patients have no any actual clinical manifestations during the entire course of the disease[18]. Asymptomatic cases, however, particularly those with no history of contact with a known SARS-CoV-2, are hard to identify. There are several case reports of SARS-CoV-2 transmission from asymptomatic individuals[8,9,13,19],

including a report of presumed transmission by asymptomatic carriers with normal chest computed tomography (CT)[20]. Together, these traits make control of SARS-CoV-2 very difficult.

However, the exact profile of these asymptomatic cases and their role within the wider epidemic are unclear. It is important to understand the proportion of asymptomatic or mildly ill cases and their role in driving the epidemic[21]. Since many SARS-CoV-2 infections are asymptomatic, subclinical or very mild the hallmarks and course of asymptomatic infection warrants for further investigation[22-24]. Our goal was to document the characteristics of asymptomatic infections and identify factors associated with asymptomatic infection, enabling the formulation of corresponding strategies and control measures.

Materials and Methods

Data sources

We conducted a retrospective study focusing on the characteristics and length of RT-PCR positivity and associated hospitalization of confirmed asymptomatic cases of SARS-CoV-2 in northeast region of Chongqing almost in the Chongqing Three Gorges Center Hospital and Wanzhou district Hospital since January 2020.

Active contact tracing in China includes nasopharyngeal swab diagnostic testing of all contacts regardless of symptoms. In accord with Chinese Guidelines for the investigation and management of close contacts of COVID-19 cases, close contacts were defined as people who had not taken effective protection while in close contact with suspected or confirmed cases 2 days prior to symptom onset or, if the case was asymptomatic, 2 days before sampling[25]. We screened close contacts from January through March 2020 in northeast Chongqing by real time reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs. Only

patients with an RT-PCR-confirmed infection and without any apparent symptoms, including (but not limited to) cough, fever, short of breathless and muscle soreness were enrolled in this study.

These individuals were identified through close symptomatic contacts in both the clinic and the community. In accord with China's prevention and control policy, all RT-PCR positive cases were hospitalized and treated whether they have symptoms or not. We monitored asymptomatic individuals daily during hospitalization to document the development of any signs and symptoms. We recategorized patients who were asymptomatic at baseline to symptomatic if they reported any symptoms. Case definitions of confirmed human infection with SARS-Cov-2 are in accordance with the interim guidance from the World Health Organization. Following a positive SARS-Cov-2 nucleic acid test, a chest CT scan was done[26]. Individuals were then divided to two groups by chest CT scan: a group with changes visible on the radiographic imaging, called asymptomatic COVID-19 patients, and a group without any detectable imaging changes, called asymptomatic with normal chest CT. During hospitalization, all participants, regardless of group, had follow-up chest CT scans every 4 to 5 days until discharge. Individuals initially allocated to the asymptomatic with normal chest CT group were immediately reallocated to the asymptomatic COVID-19 patient group if a new abnormal finding was detected on any chest CT during hospitalization.

With the approval of the ethics committee, we collected both epidemiological data and medical reports for these two groups. Epidemiological data collection was achieved by interviewing each patient and their family members, including the dates and times of close contact with (working together, living or gathering) or to exposure individuals from the affected area (not only Wuhan) with confirmed or suspected SARS-CoV-2 infection. All the data were checked by two researchers. If there existed anything ambiguous, we consulted the attending physician as soon as possible.

Laboratory tests

Diagnosis was made by nasopharyngeal swab and RT-PCR to confirm SARS-CoV-2 infection. The virus detection protocol was repeated on subsequent days until a negative nucleic acid was obtained on two consecutive occasions. Other laboratory tests were conducted at admission.

Treatment

Per standard Chinese protocol, all patients were treated with putative antiviral agents on admission [25]. Fifty eight of the 63 in the asymptomatic COVID-19 cohort received antiviral treatment with α-Interferon inhalation (5million units twice daily) and Lopinavir/ Ritonavir oral (400 mg/ 100 mg twice daily) with 10mg Thymosin injection every day to improve immunity. Of the remaining 5 patients, one received Lopinavir/ Ritonavir (400 mg/ 100 mg twice daily), Arbidol (200 mg three times daily), α-Interferon inhalation (5million units twice daily), Thymosin and Ribavirin (500mg twice daily) (Figure 1). RT-PCR testing was repeated 5 to 7 days after treatment. Patients were discharged after receiving two negative results at least 24 hours apart and a normal chest CT scan [24].

Statistical analysis

Continuous variables were expressed as the means and standard deviations or medians with interquartile ranges. Categorical variables were summarized as the counts and percentages in each category. T- tests or Mann-Whitney U tests were applied to continuous variables, and Fisher's exact tests or Pearson Chi-Square tests were used for categorical variables. All analysis was conducted with SPSS 26.0.

Results

General condition

Due to active contact tracing of index cases using RT-PCR screening 279 cases were diagnosed with SARS-CoV-2 infection. Among them, 63 had no symptoms either at the time of diagnosis or throughout hospitalization. However, 29 of the 63 cases had abnormal chest CT findings while the remaining 34 had normal chest CTs. In total, the mean age was 39.3 years (standard deviation: 16.5). The mean age of cases with abnormal chest CT was 46.3 years (SD: 16.8) compared to 33.4 years (SD: 13.8) of cases with normal chest CT ($p<0.05$). Overall, more than half of the 63 cases were male (34, 54%); however, 62.1% of patients with abnormal CT findings were male. Comorbid conditions were present in only 8/63 cases (12.7%); 6 (20.7%) in asymptomatic COVID-19 patients and 2 (6.1%) in asymptomatic cases with normal chest CT (Table 1). All of these comorbidities were reported to be very mild by the patients' clinicians.

Regarding potential sources of infection, less than a third (n=17, 27%) of cases had made short trips to Hubei province and none had been to Huanan seafood market. Six cases in the asymptomatic with normal chest CT group could not provide the exact date of close contact with someone with confirmed or suspected SARS-CoV-2 infection. Of the remaining 57 cases, the mean time from exposure to illness onset was 16.0 days (SD: 6.6). In asymptomatic COVID-19 patients this period was 13.4 days (SD: 6.3), while in asymptomatic cases with normal chest CT it was 18.7 days (SD: 5.8) ($p<0.05$). Among the 63 cases there were 18 cases of familial clustering in which 9 cases (14.3%) transmitted the virus to others outside their families, 4 from the asymptomatic COVID-19 patients and 5 from the asymptomatic cases with normal chest CT (Figure 1).

Clinical Laboratory and Immunologic Findings

On admission, only 4 of the 63 (6.3%) cases showed leucopenia (white blood cell count $<4\times10^9$/L) and 4 (6.3%) showed leukocytosis (white blood cell count $>10\times10^9$/L). All the cases had a neutrophil count within the normal range. Eight (12.7%) cases had low level lymphocyte count ($<1.0\times10^9$/L), including six (20.7%) asymptomatic COVID-19 patients and two (5.9%) asymptomatic with normal chest CT. Thirty-five of the 63 cases were given procalcitonin tests, with a mean of 0.029 ng/ml (range from 0.02 to 0.039) indicating a level within the normal range. Almost half of the 63 cases were tested for cytokines such as IL-6, IL-10 and IL-17, liver and kidney function, with all showing normal results. In all of these laboratory tests, the two imaging groups showed no significant difference (Table 2).

Clinical outcome

Fitness for discharge was based on two consecutive negative RT-PCR tests of oropharyngeal swabs and a normal chest CT scan. All patients were discharged, and no one died. The median time between the initial positive RT-PCR test and discharge was significantly longer in asymptomatic COVID-19 patients than in asymptomatic patients with normal chest CT, 13.0 and 10.4 days, respectively ($p<0.05$; Figure 2).

Discussion

The number of SARS-CoV-2 infections is still rising rapidly in many parts of the world, and asymptomatic infections likely play a large role in transmission [22]. To our surprise, 23% of those identified with SARS-CoV-2 infection, including those with abnormal chest CT scans on admission, were completely asymptomatic throughout their infections—a much higher proportion than previously reported[18]. The high proportion may be related to the extensive and strict close

contact screening policy adopted locally resulting in early detection and treatment of cases. This finding suggests that there are actually more asymptomatic COVID-19 cases than previously thought, highlighting asymptomatic cases as a noteworthy source of infection. A recent study reported that the viral load in asymptomatic patients is similar to that in symptomatic patients, further underscoring the transmission potential of these asymptomatic patients[27]. Together these results suggest that strict isolation and screening should be carried out in all asymptomatic close contacts. CT scans can assist in the detection of asymptomatic pneumonia, but cannot identify asymptomatic cases with normal chest CT. If nucleic acid testing were reserved only for suspected patients with obvious symptoms, many contacts with mild symptoms or asymptomatic would be missed—as would their contacts.

Since there are no obvious symptoms, asymptomatic cases typically remain undiagnosed for a relatively long time. In our study the mean latency between close contact and diagnosis was 16.0 days, with a maximum of 29 days. This suggests that RT-PCR screening should be undertaken even if an individual shows no symptoms more than 14 days after close contact with an infected person. In asymptomatic patients, patients whose CT scans show signs of pneumonia are typically diagnosed earlier than those without such signs.

Because the pathogenesis of COVID-19 is not well understood, all nucleic acid positive cases received antiviral treatment to prevent progression of the disease. Although the efficacy of antiviral therapy is still unknown, it is possible that treatment prevented the progression of disease in this cohort. Asymptomatic COVID-19 patients with abnormal chest CTs showed improvement over time, suggesting that these patients may have benefitted from the antiviral therapy. Even with antiviral therapy the average time for viral nucleic acid testing assays to return to negative in the asymptomatic COVID-19 patients after treatment was 13 days, which is not shorter than time reported for mild symptomatic patients[12]. However, cases with abnormal chest CT took significantly longer to become RT-

PCR negative than those without chest CT abnormalities. These characteristics indicate that asymptomatic COVID-19 cases are important recessive sources of infection. Thus, diagnosing all SARS-CoV-2 infections cases including the very mild, subclinical or asymptomatic as soon as possible and immediately isolating them is likely to be critical to cutting off the source of infection. Although they have no symptoms or even no abnormal chest image, they spread the virus, causing infection and morbidity[20].

We found that 18 of the 63 asymptomatic cases (28.6%) had infection associated with familial clustering, indicating that asymptomatic infections can be identified through screening family members of index case. The high proportion may be related to the extent and length of close contact, as well as the relative ease of tracking and screening family members [8,9]; however, it is sometimes difficult to tell who transmitted the virus, the asymptomatic case or the infected family member [8]. It also suggests that occult transmission of SARS-CoV-2 may exist. Only 14% of the asymptomatic cohort infected others, occurring equally between those with and without chest CT abnormalities. But it is certain that there are still a few asymptomatic cases that can cause transmission[28]. Serum antibody tests may provide a low cost and rapid method for screening and could come to play an important role in the auxiliary diagnosis of SARS-CoV-2 infection[29].

As a group, the asymptomatic cases in our study were younger and had fewer comorbidities compared to severe cases[11,12]. Research shows that the adaptive immune response against the virus in people with asymptomatic infection is stronger than in those with symptomatic infection[30,31]. Asymptomatic individuals without imaging abnormalities are younger than those with pneumonia. From our results, it seems that young individuals with normal immune function and without comorbidities are more likely to become asymptomatically infected.

All patients in the study, with and without abnormal chest CTs, steadily improved and were discharged smoothly after testing negative by RT-PCR. However, we do not know whether these asymptomatic cases, particularly those who had developed

an abnormal chest CT, would have progressed to more severe disease without early antiviral treatment. The results also suggest the need for rigorous randomized controlled studies to determine what antiviral therapies are safe and effective and whether early antiviral treatment for asymptomatic RT-PCR+ individuals can prevent progression of disease and/or the length of time cases remain RT-PCR+. Finally, SARS-CoV-2 vaccine study designs should not simply use symptomatic COVID-19 as an endpoint, but include asymptomatic infections as well.

This study has several limitations. First, only 63 asymptomatic cases were included; as such it may be that we found no other associated epidemiologic factors due to sample size. Second, we used a qualitative RT PCR test and could not quantitate viral load; thus, asymptomatic cases with low viral load may have been missed. Third, a precise incubation period and transmissibility are difficult to document due to the concealed nature of asymptomatic infection. Finally, our study does not provide a mechanistic explanation for asymptomatic status; a study linking asymptomatic status with differences in individual immu1nity, virus serotypes, viral load or other factors would contribute useful insights.

In conclusion, here we provide an initial assessment of epidemiologic characteristics of asymptomatic infections of SARS-CoV-2. Early identification of SARS-CoV-2 cases with subsequent isolation and treatment may contribute to decreased transmission and mortality.

Contributors

YH and JlX had the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YW, JT, YQ, TX, JhX, YC, JrL and JlX contributed to data acquisition**.** YH, YW, ESH, and JT contributed to writing of the report. JhL contributed to the statistical analysis. All authors contributed to data analysis, or data interpretation, and reviewed and approved the final version.

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With the permission of the corresponding authors, we can provide participant data without names and identifiers. Data can be provided after the Article is published. Once the data can be made public, the research team will provide an email address for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided. This study was reviewed and approved by the Medical Ethical Committee of Daping Hospital and Chongqing Three Gorges Central Hospital.

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Declaration of interests

The authors declare no conflict of interest.

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Figure Legends

Figure 1 Clinical course and treatments of the 63 asymptomatic patients with SARS-CoV-2

Figure 2 Outcomes and mean and median for length of hospital stay of the 63 asymptomatic patients with SARS-CoV-2

Table 1 Personal and clinical characteristics of 63 asymptomatic patients with SARS-CoV-2

Table 2 Laboratory findings in 63 asymptomatic patients with SARS-CoV-2

Table 1 Personal and clinical characteristics of 63 asymptomatic patients with coronavirus disease 2019 (covid-19)

Characteristics	All asymptomatic patients (n=63)	Chest radiology		P Value
		Normal chest CT (n=34)	Abnormal chest CT (n=29)	
Age (years)	39.30±16.45	33.36±13.81	46.26±16.79	0.001
Age groups (years):				0.003
≤18	7(11.1%)	5(14.7%)	2(6.9%)	
19-40	25(39.7%)	19(55.9%)	6(20.7%)	
41-65	28(44.4%)	10(29.4%)	18(62.1%)	
≥66	3(4.8%)	0	3(10.3%)	
Sex:				0.233
Male	34(54%)	16(47.1%)	18(62.1%)	
Female	29(46%)	18(52.9%)	11(37.9%)	
Coexisting conditions:				0.103
Any	53(84.1%)	31(91.2%)	22(75.9%)	
Hypertension	3(4.8%)	0	3(10.3%)	
Cardiovascular disease	1(1.6%)	0	1(3.4%)	
Diabetes	1(1.6%)	0	1(3.4%)	
COPD	1(1.6%)	1(2.9%)	0	
Systemic lupus erythematosus	1(1.6%)	0	1(3.4%)	
Gout	1(1.6%)	1(2.9%)	0	
Chronic gastritis	2(3.2%)	1(2.9%)	1(3.4%)	
Exposure history in Hubei:				0.504
Yes	17(27%)	8(23.5%)	9(31%)	
No	46(73%)	26(76.5%)	20(69%)	
Familial cluster	18(28.6%)	11(32.4%)	7(24.1%)	0.472
Days from exposure to diagnosis	15.98±6.55 (n=57)	18.68±5.79 (n=28)	13.38±6.25 (n=29)	0.002
Number of others infected:				1.000
No	54(85.7%)	29(85.3%)	25(86.2%)	
Yes	9(14.3%)	5(14.7%)	4(13.8%)	

Table 2 Laboratory findings in 63 asymptomatic patients with covid-19

Variables	All asymptomatic patients (n=63)	Chest radiology		P Value
		Normal chest CT (n=34)	Abnormal chest CT (n=29)	
White blood cell count (×10^9/L)	6.81±1.98	7.10±2.04	6.47±1.88	0.207
White blood cell count (×10^9/L):				0.854
<4	4(6.3%)	2(5.9%)	2(6.9%)	
4-10	55(87.3%)	29(85.3%)	26(89.7%)	
>10	4(6.3%)	3(8.8%)	1(3.4%)	
Neutrophil count (×10^9/L)	4.59±1.78	4.91±1.89	4.21±1.59	0.122
Lymphocyte count (×10^9/L)	1.61(1.24-1.92)	1.66(1.35-1.95)	1.59(1.19-1.93)	0.490
Lymphocyte count (×10^9/L):				0.129
<1.0	8(12.7%)	2(5.9%)	6(20.7%)	
≥1.0	55(87.3%)	32(94.1%)	23(79.3%)	
CD4+ T lymphocytes (cells/ul)	566(371-762) (n=36)	653(460-857) (n=8)	549(332-732) (n=28)	0.313
CD8+ T lymphocytes (cells/ul)	322(252-501) (n=36)	410(277-614) (n=8)	317(229-489) (n=28)	0.304
Procalcitonin (ng/mL)	0.029(0.02-0.039) (n=35)	0.036(0.024-0.045) (n=8)	0.028(0.02-0.039) (n=27)	0.312
albumin	43.2(41.4-45.4) (n=36)	43(40.4-45.4) (n=9)	43.2(41.4-45.4) (n=27)	0.534
Alanine aminotransferase (U/L)	16.8(12.7-28.2) (n=36)	15.1(9.9-22.3) (n=9)	17.4(13.2-30.4) (n=27)	0.250
Aspartate aminotransferase (U/L)	18.8(14.8-22.6) (n=36)	19.3(13-22.5) (n=9)	18.7(15.1-23) (n=27)	0.511
Blood urea nitrogen (mmol/L)	4.5(3.7-5.2) (n=36)	4.5(3.7-4.9) (n=9)	4.4(3.7-5.5) (n=27)	0.728
Creatine (μmol/L)	64(53-77) (n=36)	54(46-79) (n=9)	65(55-75) (n=27)	0.454
IL-6 (pg/mL)	3.71(1.94-5.46) (n=33)	4.97(3.19-6.55) (n=6)	2.72(1.76-4.48) (n=27)	0.430
IL-10 (pg/mL)	2.62(2.34-3.14) (n=33)	2.68(2.57-2.97) (n=6)	2.56(2.25-3.19) (n=27)	0.484
IL-17 (pg/mL)	1.38(1.18-1.63) (n=33)	1.37(1.31-1.49) (n=6)	1.43(1.13-1.69) (n=27)	0.981

Figure 1

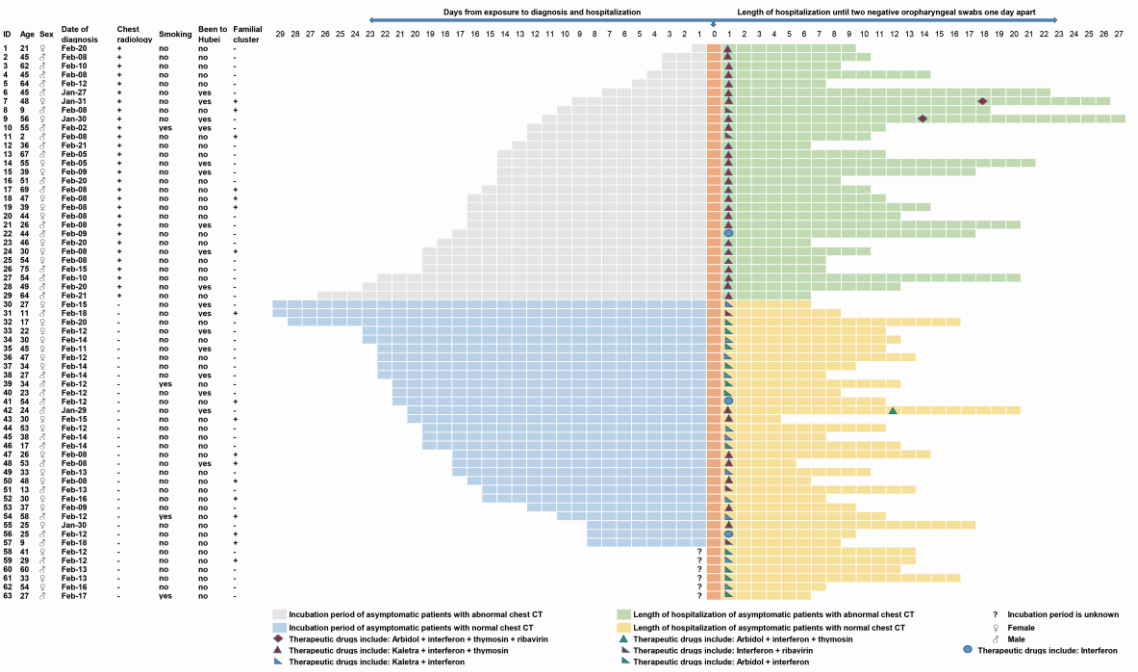

Figure 2