Analysis of moderate and severe cases of novel coronavirus disease (COVID-19) versus influenza A (H1N1)

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Abstract

Background To analyse the clinical characteristics, laboratory tests, and imaging findings of severe cases of coronavirus disease 2019 (COVID-19) versus severe cases of influenza A (H1N1).

Methods We retrospectively analysed the clinical data of moderate and severe COVID-19 and H1N1 cases between January 23 and February 23, 2020.

Results A total of 33 COVID-19 cases had a clear history of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with an incubation period of 11.12 ± 7.47 days. A total of 29 H1N1 cases were included in this study. Most cases were sporadic, with an incubation period of 3.67 ± 0.82 days (P = 0.002). The age at onset was 19.79 ± 23.88 years for H1N1 and 43.48 ± 17.82 years for COVID-19 (P < 0.001). For H1N1, common clinical symptoms were high fever and myalgia. The time of disease progression from moderate to severe was 13.60 ± 5.64 days for COVID-19 and 5.25 ± 2.36 days for H1N1 (P = 0.035). Laboratory tests showed that white blood cells (WBC), neutrophils (N), lactate dehydrogenase (LDH), C-reactive protein (CPR), and procalcitonin (PCT) were significantly higher in severe H1N1 cases than in severe COVID-19 cases. D-dimer (DD) was 1.43 ± 1.19 μg/mL in the COVID-19 group, which was higher than that in the H1N1 group (0.88 ± 0.32 μg/mL, P = 0.013). High-resolution computed tomography (CT) showed severe COVID-19 cases presented mainly interstitial involvement, shown by large ground-glass opacities, whereas severe H1N1 cases presented both interstitial and parenchymal involvement, especially parenchymal involvement. All the COVID-19 patients survived to discharge, and one H1N1 patient died.

Conclusion Compared with H1N1 patients, COVID-19 patients had a clear history of exposure to SARS-CoV-2, were older, presented milder clinical symptoms and a slower progression, and rarely had bacterial infections. Most H1N1 patients had sporadic H1N1 with an acute onset, high fever, and rapid progression; secondary bacterial infection was an important cause of disease aggravation.

Background

The outbreak of coronavirus disease 2019 (COVID-19) has become a public health emergency of international concern (PHEIC). Most COVID-19 cases are characterized by pneumonia [1–3]. The International Committee on Taxonomy of Viruses has named the virus responsible for this outbreak severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is highly infectious and has spread to other regions of China (outside Hubei) and to other countries. Currently, the Chinese government has included COVID-19, an acute respiratory infectious disease, in the list of category B infectious diseases in the *Law of the People's Republic of China on Prevention and Treatment of Infectious Diseases*. Measures for category A infectious diseases have been implemented. As of March 20, more than 70 000 confirmed cases were reported in China, and more than 680 000 cases were reported worldwide [4].

Although the disease is highly infectious, most COVID-19 cases are mild or asymptomatic, and approximately 20% progress to severe cases. In most cases, initial symptoms are fever and cough, similar to those of influenza [5–6]. Winter and spring are also peak seasons for influenza, such as influenza A (H1N1), which manifests as fever, headache, and cough. COVID-19 may be misdiagnosed as H1N1 due to lack of effective early screening tools, which may increase the risk of SARS-CoV-2 exposure for medical staff and in the community. On the other hand, over-diagnosing suspected cases as COVID-19 will cause misallocation of limited medical resources, increase the risk of cross-infection among pneumonia patients, and cause unnecessary panic and waste [7–8].

In this study, we analysed the epidemiological data, clinical diagnosis and treatment methods, laboratory tests, and factors of disease progression in COVID-19 patients versus H1N1 patients in order to provide a reference for the diagnosis of COVID-19, the differential diagnosis of COVID-19 and H1N1, and the early detection and treatment of potential severe cases.

Materials And Methods

General information

We collected the clinical data of 33 COVID-19 cases and 29 H1N1 cases treated at the First Affiliated Hospital of Wannan Medical College, the Fourth People's Hospital of Maanshan, and Chizhou People's Hospital between January 23 and February 23, 2020. COVID-19 was diagnosed according to the criteria in the *Guidelines for Diagnosis and Treatment of COVID-19* (Trial, Edition 6) [9]. Twenty patients were men, and 13 were women. Five of them had severe COVID-19. H1N1 was diagnosed according to the *Guidelines for Diagnosis and Treatment of Influenza* (2019) [10]. Nineteen patients were men, and 10 were women. Four of them had severe H1N1.

Methods

The following methods were used in this study: Detailed medical history, especially epidemiological data, history of past illness, and personal history; clinical data; laboratory tests, including complete blood count, urinalysis, faecal analysis, procalcitonin (PCT), C-reactive protein (CRP), liver and kidney function, myocardial enzymes, troponin, and coagulation; pathogen tests, including throat swabs for SARS-CoV-2 nucleic acid testing, influenza virus nucleic acid testing, and antigen testing for the detection of H1N1; imaging studies, such as chest high-resolution computed tomography (HR-CT).

Statistical analysis

SPSS v 20.0 was used for statistical analysis. Data are expressed as frequency (n) or mean ± standard deviation. Measurement data were analysed with the non-parametric test, and categorical variables were

analysed with the c^2 test.

Results

Epidemiological data for COVID-19 versus H1N1

The COVID-19 patients were aged 14 to 85 years (mean: 43.48 ± 17.82 years), and the H1N1 patients were aged 21 months to 83 years (mean: 19.79 ± 23.88 years). The difference was statistically significant (P < 0.001). H1N1 was significantly more prevalent than COVID-19 in children; the sample included 19 H1N1 patients under 14 years of age. Both COVID-19 and H1N1 were more common in men than in women, although no significant difference in sex composition was observed between the COVID-19 group and the H1N1 group. Of the 33 patients with COVID-19, 32 had a clear history of exposure to SARS-CoV-2. Among them, 19 were from Wuhan, 12 had had direct contact with confirmed cases (two patients had each infected five individuals in the same village, resulting in clusters of cases), and one had had contact with an asymptomatic individual in the same village who had recently returned from Wuhan. Four patients were from two families (mother and child). The incubation period was 11.12 ± 7.4 days. Most of the H1N1 cases were sporadic and had an incubation period of 3.67 ± 0.82 days, which was significantly shorter than the incubation period for COVID-19 (P = 0.002). See Table 1.

Clinical characteristics

The COVID-19 patients presented fever, cough, and fatigue; all of these symptoms were more common in H1N1 patients, especially high fever (P < 0.001). Low and intermediate fever were more common in COVID-19. Myalgia was mainly observed in H1N1. No significant between-group difference was observed in other respiratory symptoms or in gastrointestinal symptoms. See Table 1.

Laboratory tests

Laboratory tests for moderate cases

For moderate cases, laboratory tests showed that the absolute neutrophil (N) count was higher in the H1N1 group than in the COVID-19 group. No significant between-group difference was observed in white blood cells (WBC), absolute lymphocyte count, absolute eosinophil count, lactate dehydrogenase (LDH), CRP, PCT, or D-dimer (DD) (Table 2).

Severe cases

Among the 33 COVID-19 cases, five were severe cases, including two men and three women aged 54.60 ± 6.73 years. Among the 24 H1N1 cases, four were severe, including two men and two women aged 57.50 ± 9.43 years. The age difference did not reach statistical significance. In the COVID-19 group, two patients had diabetes, and one had chronic gastritis. In the H1N1 group, one patient had chronic obstructive pulmonary disease, and one had lymphoma, diabetes, and Sjogren's syndrome. The duration of disease progression from moderate to severe was 13.60 ± 5.64 days in the COVID-19 group, which was longer than the duration of progression in the H1N1 A group (5.25 ± 2.36 days, P = 0.035). The WBC count (especially neutrophils) was higher in severe H1N1 cases than in severe COVID-19 cases. The absolute eosinophils count was 0 in the severe cases and lower in the moderate cases in both groups. See Table 3. No significant between-group difference was observed in LDH. Inflammatory indicators were higher in severe H1N1 cases than in severe COVID-19 cases (CRP, P = 0.001; PCT, P = 0.009). DD was 1.43 ± 1.19 μg/mL in the COVID-19 group, which was higher than that in the H1N1 group (0.88 ± 0.32 μg/mL, P = 0.013). Sputum culture was negative in severe COVID-19 cases and was positive in two patients with severe H1N1 (*Staphylococcus aureus*, n = 1, *Klebsiella pneumoniae*, n = 1).

Imaging studies

Given that both COVID-19 and H1N1 are viral infections, CT showed similar findings in the early stage of moderate cases between the two groups; the findings were single or multiple small, patchy ground-glass opacities (GGOs), which may be missed in this stage (Figures 1A, 1B). In the late stage of moderate cases and severe cases, CT findings differed between the two groups. In the H1N1 cases, CT showed interstitial and parenchymal involvement (especially parenchymal involvement) as patchy or large high-attenuation opacities along the bronchi and without clear boundaries, sometimes with the tree-in-bud sign (Figure 1C). In the COVID-19 cases, CT showed primarily interstitial involvement as large GGOs with slightly dilated bronchi and sometimes consolidation or fibrosis (Figure 1D). In some cases, however, it was difficult to diagnose the cause based on imaging findings, and clinicians had to consider clinical signs and symptoms.

Treatment and prognosis

Most of the COVID-19 patients received anti-viral therapy with lopinavir/ritonavir plus interferon α-2b nasal spray; two patients received umifenovir (Arbidol) plus interferon α-2b spray. The treatment time was seven to ten days. Five patients with severe COVID-19 also received high-flow oxygen therapy. All patients survived to discharge, with no disease progression (to critical status) or death. The H1N1 patients received anti-viral therapy with oseltamivir for five days. Patients with severe H1N1 also received antibiotic therapy. Two patients with severe H1N1 received mechanical ventilation due to respiratory failure, and one of these patients received extracorporeal membrane oxygenation (ECMO); one patient survived to discharge, and the other died.

Discussion

Six species of coronavirus are known to cause infections in human, including α 229E, NL63, β OC43, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-COV). SARS-COV and MERS-COV can cause severe acute respiratory syndrome and have mortality rates of 10% and 37%, respectively [11–12]. The outbreak that started in Wuhan was caused by a novel coronavirus [13]. Gene sequencing showed that the novel coronavirus is 79.5% homologous to SARS-COV. It is a betacoronavirus and is the seventh known coronavirus that can infect humans. It is highly homologous to bat coronavirus (> 85%), suggesting that wild animals such as bats may be the natural host of this novel coronavirus [14].

This study showed that almost all of the COVID-19 patients treated in Wuhu, Maanshan, and Chizhou had an history of exposure to SARS-CoV-2. The patients were from Wuhan or had had direct contact with confirmed patients who had recently returned from Wuhan. Only one patient developed symptoms after contact with an asymptomatic individual who had recently returned from Wuhan. Two patients had each infected five other individuals in the same village with whom they had close contact, resulting in clusters of cases. Moreover, there were two mother-child pairs in the COVID-19 group. The data indicate significant local clusters of cases. A history of exposure to SARS-CoV-2 is very important for the diagnosis of local COVID-19 cases. Most H1N1 patients were sporadic, except four patients who had untreated family members with similar symptoms. A detailed history of exposure to SARS-CoV-2 is very important for the early differential diagnosis of COVID-19 and H1N1.

In both groups, there were more men than women, although the difference in sex composition did not reach statistical significance. The COVID-19 patients were aged 14 to 85 years (mean: 43.48 ± 17.82 years), and the H1N1 patients were aged 21 months to 83 years (mean: 19.79 ± 23.88 years), and the difference was statistically significant ($P < 0.001$). H1N1 was more prevalent than COVID-19 in children, and 19 H1N1 patients were under 14 years of age. These data indicate that COVID-19 is more common among middle-aged men; H1N1 infects younger populations and is more common in children. The incubation period was 11.12 ± 7.4 days for COVID-19, which was significantly longer than that for H1N1 (3.67 ± 0.82 days, $P = 0.002$). In both groups, common clinical symptoms were fever, cough, fatigue, some white sputum, stuffy nose, runny nose, sore throat, and, rarely, diarrhoea. Myalgia was significantly more common in H1N1 than in COVID-19. H1N1 was characterized by an acute onset, high fever, and rapid progression (time from onset to severe status: 5.25 ± 2.36 days). COVID-19 was characterized by a low or intermediate fever (or no fever, in some cases) and a significantly slower progression (13.60 ± 5.64 days). All four severe cases of H1N1 were related to a secondary bacterial infection. For severe cases, WBC, neutrophils, LDH, CPR, and PCT were significantly higher in the H1N1 group than in the COVID-19 group. Sputum culture was positive for *S. aureus* in one H1N1 patient. H1N1 infection can cause respiratory epithelial injury, making it easier for methicillin-resistant *S. aureus* (MRSA) to take hold and cause a secondary bacterial infection [15–17]. Five severe cases of COVID-19 were considered related to disease progression because PCT and WBC had been normal. DD was 1.43 ± 1.19 μg/mL in the COVID-19 group, which was higher than that in the H1N1 group (0.88 ± 0.32 μg/mL, $P = 0.013$). This

finding may be related to COVID-19-associated coagulation abnormalities [17–18]. Among the nine patients with severe COVID-19 or H1N1, five had underlying disease, which was an important cause of disease progression [19–20]. Five patients with severe COVID-19 received anti-viral therapy and high-flow oxygen therapy; all of these patients survived to discharge, with no further progression (to severe status) or death. Two patients with severe H1N1 received antiviral and antibiotic therapy as well as mechanical ventilation due to respiratory failure, and one of these patients received ECMO; finally, one patient survived to discharge, and the other died.

In the early stage of moderate disease, CT presented similar findings, such as single or multiple small, patchy GGOs, making it difficult to differentiate between COVID-19 and H1N1. Moreover, lesions may be missed on regular CT due to the small lesion size, indicating that HR-CT is required to improve the detection rate. In the late stage of moderate and severe disease, CT showed more specific characteristics, which may help to distinguish between COVID-19 and H1N1. CT presented primarily interstitial involvement in the COVID-19 group and interstitial and parenchymal involvement (especially parenchymal involvement) in the H1N1 group. Moreover, CT showed slightly higher-attenuation opacities in the H1N1 group than in the COVID-19 group [20–21].

This study shows that most local COVID-19 cases (outside Hubei) were imported cases that resulted from close contact with individuals who had recently returned from Hubei, sometimes family members, suggesting that COVID-19 is primarily transmitted by respiratory droplets or close contact. Therefore, the management of imported cases and individuals who have recently returned from Hubei plays a key role in the management of local COVID-19 outbreaks. This year, most H1N1 cases have been sporadic and differ from COVID-19 in the age of onset, rate of disease progression, fever grade, secondary infection rate, and the presence of myalgia. The combination of a history of exposure to SARS-CoV-2, rapid antigen testing for the detection of H1N1, and chest imaging studies may help distinguish between COVID-19 and H1N1. For COVID-19, disease progression may be related to the cytokine cascade, which should be treated promptly. For H1N1, disease progression may be related to secondary bacterial infection, which should be managed with anti-infective therapy. The number of severe cases in this study sample was small. In the future, we will include more patients and analyse their epidemiological data, laboratory test results, and prognosis to further validate the results of this study.

Abbreviations

COVID-19
Coronavirus disease 2019; H1N1:influenza A; SARS-CoV-2:syndrome coronavirus 2; WBC:white blood cells;N:neutrophils; LDH:Lactate dehydrogenase; CPR:C-reactive protein; PCT:procalcitonin; DD:D-dimer; CT:computed tomography; HR-CT:High-resolution computed tomography; ECMO:Extracorporeal membrane oxygenation; GGOs:Ground-glass opacities; MRSA:Methicillin-resistant *S. aureus*

Declarations

Competing interests

The authors declare that they have no competing interests

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Author contributions

JHY designed the study. WSH, HYS and MML collected the patients data and analyzed the data and wrote the initial draft of the manuscript.. ZJW, XLX and YSC performed the statistical analysis. FL, APZ, BQ and YFZ design figures and tables. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Ethics Approval And Consent To Participate

The present study was approved by The Second Affiliated Hospital of Wannan Medical College (Wuhu, China, number:20200101) and it conforms to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all individuals in the present study.

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Tables

Table 1 Clinical Characteristics

	COVID-19 (n=33)	H1N1 (n=29)	*P* value
Age(years)	43.48 ± 17.82	19.79 ± 23.88	0.001
Sex			0.69
Male	20	19	
Female	13	10	
Incubation period (day)	11.12 ± 7.47	3.67 ± 0.82	0.002
Fever			< 0.001
> 40 ℃	0	7	
39-40 ℃	3	14	
38-38.9 ℃	7	8	
< 37.9 ℃	23	0	
Coughing	10	24	< 0.001
Expectoration	5	9	0.136
Fatigue	9	18	0.006
Myalgia	1	13	< 0.001
Diarrhoea	4	3	0.825
Vomiting	2	4	0.304
Stuffy nose	3	1	0.367
Chest tightness	6	4	0.639
Anorexia	7	6	0.96
Runny nose	3	6	0.196
Sore throat	1	3	0.242

Table 2 Laboratory Tests for Moderate Cases

	COVID-19 (n = 28)	H1N1 (n = 25)	*P* value
WBC ($\times 10^9$/L)	4.67±1.59	5.97±2.54	0.101
N %	55.12±25.40	64.74±21.02	0.259
N ($\times 10^9$/L)	3.03±1.30	4.11±2.39	0.007
L (%)	21.83±15.33	26.80±19.06	0.453
L ($\times 10^9$/L)	1.26±0.70	1.63±1.02	0.148
E ($\times 10^9$/L)	0.15±0.21	0.10±0.14	0.754
RBC ($\times 10^{12}$/L)	4.38±0.34	4.63±0.51	0.110
HGB (g/L)	122.20±33.58	126±18.87	0.703
PLT ($\times 10^9$/L)	152.05±53.72	187.64±74.23	0.104
LDH (U/L)	227.20±75.34	268.08±90.53	0.153
CPR (mg/L)	27.90±36.14	63.68±104.89	0.081
PCT (ng/mL)	1.98±6.48	1.18±1.88	0.604
DD (μg/mL)	0.35±0.69	0.38±0.84	0.463

WBC=white blood cell, N=neutrophil, L=lymphocyte, E=eosinophil, RBC=red blood cell, HGB=hemoglobin, PLT=platelet, LDH=lactate dehydrogenase, CPR= C-reactive protein, DD= D-dimer

Table 3 Severe Cases

	COVID-19 (n = 5)	H1N1 (n = 4)	*P* value
Age (years)	54.60 ± 6.73	57.50 ± 9.43	0.464
Duration of disease progression from moderate to severe (days)	13.60 ± 5.64	5.25 ± 2.36	0.035
WBC ($\times 10^9$/L)	7.40±3.14	13.13±6.41	0.241
N ($\times 10^9$/L)	6.45±2.96	11.78±5.62	0.298
L ($\times 10^9$/L)	0.63±0.25	0.62±0.23	0.518
E ($\times 10^9$/L)	0.00	0.00	
RBC ($\times 10^{12}$/L)	4.47±0.44	4.75±0.50	0.482
HGB (g/L)	123.00±9.77	112.50±15.63	0.271
PLT ($\times 10^9$/L)	187.60±18.42	157.50±44.10	0.139
LDH (U/L)	291.75.20±82.96	367.20±141.12	0.338
CPR (mg/L)	105.30±17.83	303.51±77.28	0.001
PCT (ng/mL)	0.22±0.56	58.78±8.61	0.009
DD (μg/mL)	1.43±1.19	0.88±0.32	0.013
Sputum culture (n)	0	2	

WBC=white blood cell, N=neutrophil, L=lymphocyte, E=eosinophil, RBC=red blood cell, HGB=hemoglobin, PLT=platelet, LDH=lactate dehydrogenase, CPR= C-reactive protein, DD= D-dimer

Figures

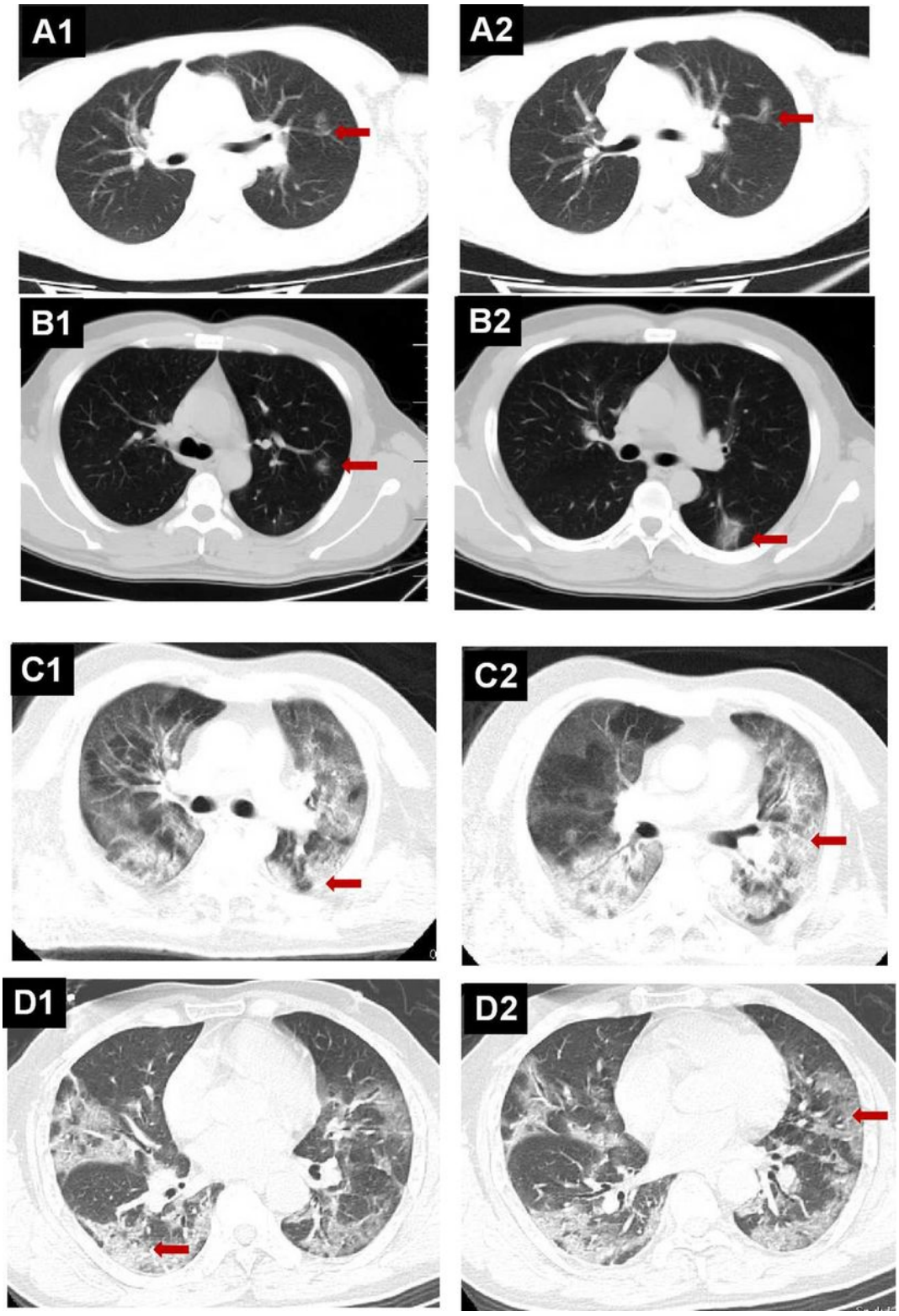

Figure 1

High-Resolution Computed Tomography of the Chest. A: boy with H1N1 pneumonia: small, patchy ground glass opacities (GGOs) in the apicoposterior segment of the left upper lobe (A1, A2). B: A young man with COVID-19: small, patchy GGOs in the left middle lobe (B1) and the dorsal segment of the left lower lobe (B2). C: A old man with severe H1N1 pneumonia: patchy high-attenuation opacities, mainly alveolar lesions in the lungs (C1) along the bronchi and without clear boundaries; some GGOs (C2). D: A old

woman with severe COVID-19: large GGOs in the lungs (D1, D2), mainly interstitial lesions with slightly dilated bronchi, and some partial consolidation in the right lower lobe (D1).