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Case report

Clinical course and findings of 14 patients with COVID-19 compared with 5 patients with conventional human coronavirus pneumonia

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ABSTRACT

Objective: To clarify what future problems must be resolved and how clinical findings of SARS-CoV-2 infection differ from those of cHCoV infection.

Methods: Patients and Methods Clinical characteristics of 14 patients with laboratory-confirmed Coronavirus disease 2019 (COVID-19) and 5 patients with cHCoV pneumonia admitted to our institution and treated up to March 8, 2020, were retrospectively analyzed.

Results: On admission, 10 patients had pneumonia, 5 of whom had pulmonary shadows detectable only via computed tomography (CT). During hospitalization, another patient with no pulmonary shadows on admission developed pneumonia. In total, 11 (78.6%) of the 14 patients developed pneumonia, indicating its high prevalence in COVID-19. During hospitalization, the patients' symptoms spontaneously relapsed and resolved, and gastrointestinal symptoms were frequently found. C-reactive protein values showed correlation with the patients' clinical courses. Ritonavir/lopinavir were administered to 5 patients whose respiratory conditions worsened during admission, all of whom improved. However, the pneumonia in the 6 other patients improved without antivirals. None of the 14 patients died, whereas 5 other patients with cHCoV pneumonia were in respiratory failure on admission, and one patient (20%) died.

Conclusion: Both SARS-CoV-2 and cHCoV can cause severe pneumonia. Problems for future resolution include whether antiviral agents administered in cases of mild or moderate severity can reduce the number of severe cases, and whether antivirals administered in severe cases can reduce mortality.

Funding

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1. Introduction

As cases of SARS-CoV-2 infection, termed coronavirus disease 2019 (COVID-19) by the World Health Organization, expand worldwide, the numbers of infected people and non-survivors are increasing. Although the greatest number of SARS-CoV-2 infections were initially reported from China, numerous cases are being reported worldwide. It is currently unclear how clinical findings of SARS-CoV-2 infection differ from those of conventional human coronavirus (cHCoV) infection. To better understand and adequately manage this novel threat, accumulating detailed clinical courses of infected patients and clarifying further problems obtained from physicians' experiences are required. The present study assessed detailed clinical courses of patients infected with

Abbreviations: BALF, bronchoalveolar lavage fluid; BVBs, bronchovascular bundles; cHCoV, conventional human coronavirus; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; HFNC, high-flow nasal cannula; GGOs, ground-glass opacities; SARS-CoV, severe acute respiratory syndrome coronavirus 2.

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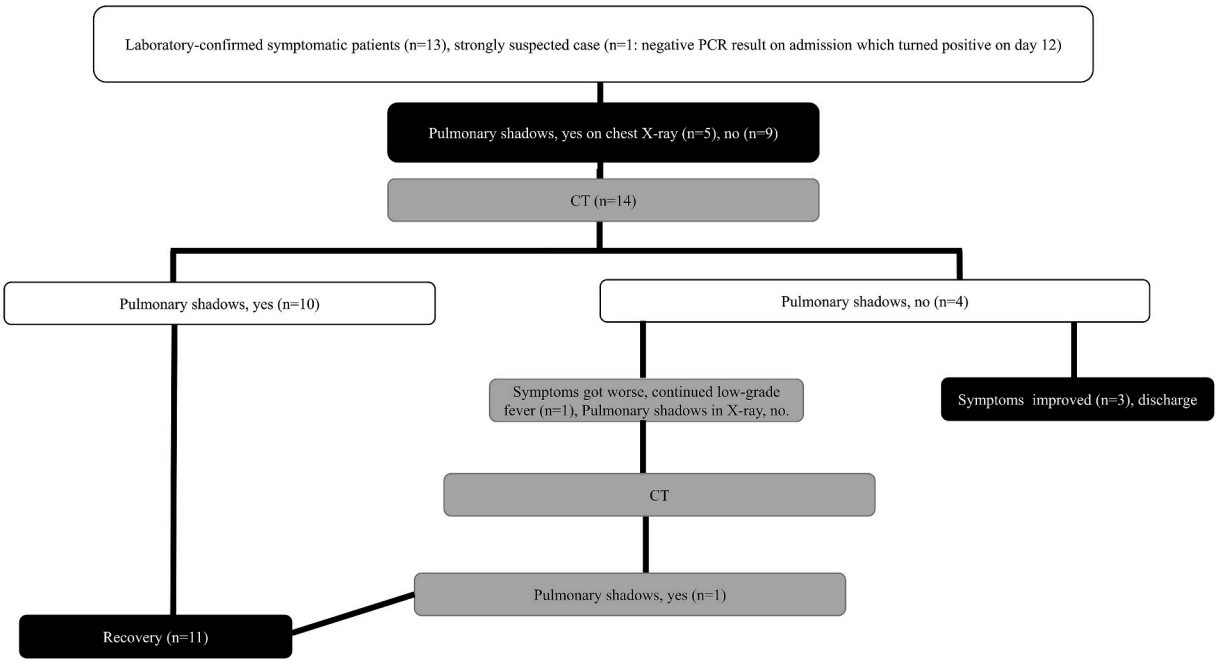


Fig. 1. Flow chart of the patients included in this study. CT = computed tomography.

SARS-CoV-2 to elucidate the differences in clinical findings between patients with pneumonia due to SARS-CoV-2 and those with cHCoV pneumonia, to review clinical characteristics of SARS-CoV-2 infections, and to suggest future problems for resolution from our experience.

1.1. Patients and methods

We retrospectively studied consecutive patients with SARS-CoV-2 infection and 5 patients with primary cHCoV pneumonia admitted to our institution from January 2010 to January 2020. SARS-CoV-2 infection was diagnosed by polymerase chain reaction (PCR) from nasopharyngeal swab specimens. cHCoV pneumonia was diagnosed by positive PCR from bronchoalveolar lavage fluid (BALF) in patients with acute bilateral infiltrates to differentiate viral pneumonia from interstitial lung diseases. This study covered patients infected with SARS-CoV-2 up to March 8, 2020. Primary viral pneumonia was diagnosed when other causative microorganisms were not detected based on results of semiquantitative culture of respiratory samples or blood, paired sera, rapid diagnostic test, paired sera, and PCR tests, as reported previously [1,2]. Severity was defined as follows [3]: Mild: mild clinical symptoms (fever <38 °C [quelled without treatment]), with/without cough, no dyspnea, no gasping, no chronic disease, and no imaging findings of pneumonia; Moderate: fever, respiratory symptoms, imaging findings of pneumonia; Severe: any of respiratory distress, respiratory rate ≥30 breaths/min, resting SpO2 <93%, or PaO2/FiO2 ≤300 mmHg. Patients with rapid progression (>50%) on CT imaging within 24 h should be managed as severe. Critical: any of respiratory failure, requires mechanical ventilatory assistance, shock, “extra pulmonary” organ failure, or requires intensive care.

Two experienced radiologists (N. T. U. M.) blinded to all clinical information independently reviewed the X-rays and high-resolution computed tomography (CT) scans. These observers assessed the presence of 4 X-ray findings: consolidation, ground-glass opacities (GGOs), and nodules with their distribution (lung fields) and shape (patchy or broad), along with 16 CT findings: consolidation and GGOs with their distribution, halo sign, inverted halo sign, cavitation, centrilobular nodules, mass, tree-in-bud sign, intralobular reticulation, honeycombing, diffuse bronchial wall thickening, pleural effusion, pneumothorax, mediastinal or hilar lymphadenopathy (minimal diameter ≥10 mm), and cardiomegaly.

Days of illness were counted from the day of disease onset. Discharge criteria were afebrile >48 h, significantly improved respiratory symptoms, and two consecutive negative results for SARS-CoV-2 nucleic acid detection at least 24 h apart.

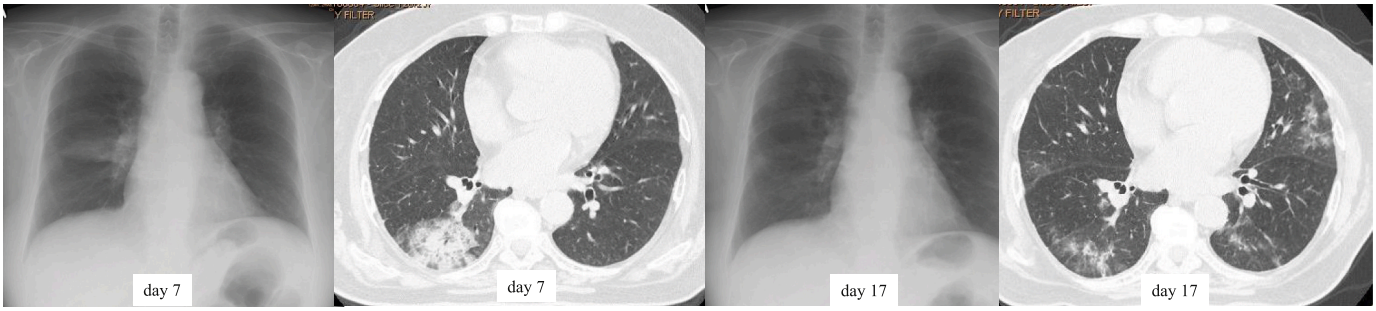
The study protocol was approved by the Ethical Committee of Saitama Cardiovascular and Respiratory Center. Signed consent forms were not obtained from 4 patients because they had returned to their home nations after recovery. Racial information and their nations were deleted to maintain patient privacy.

2. Results

Thirteen patients with laboratory-confirmed SARS-CoV-2 infection and one patient with a negative PCR test but who was strongly suspected of having SARS-CoV-2 infection were admitted to our institution, following which they underwent physician consultation, laboratory tests, and chest X-ray. Abnormal shadows were detected in 5 patients. After patient consent was obtained, all patients underwent CT scanning, which revealed abnormal shadows in 5 other patients. Thus, 10 patients were diagnosed as having pneumonia on admission. During hospitalization, another patient developed abnormal shadows on her second CT performed on day 17 from initial symptoms onset (Fig. 1). Repeat PCR of the patient whose initial test was negative was positive on day 12: thus, all 14 patients had laboratory-confirmed SARS-CoV-2 infection.

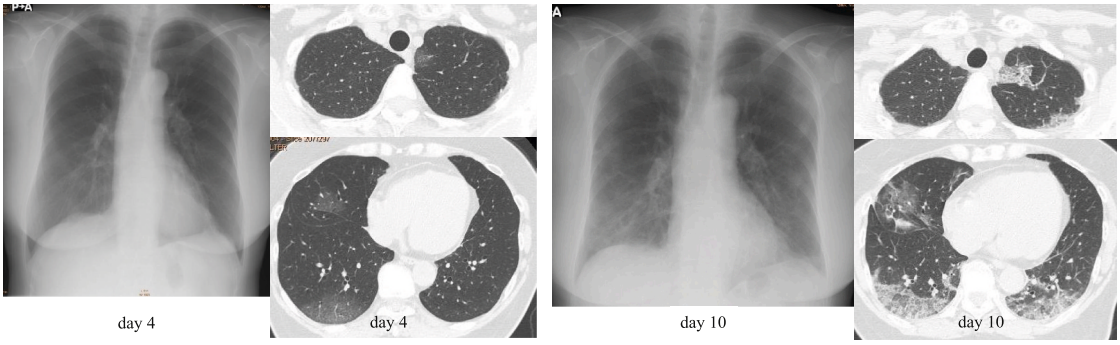
2.1. Summary of COVID-19 patients without pneumonia

Three of the 4 patients with no abnormal shadows on CT on admission and mild disease severity did not develop pneumonia throughout their clinical courses. Their symptoms, which included sore throat (n = 3), cough (n = 3), sputum (n = 3), red eyes (n = 1), and diarrhea (n = 3), gradually improved. These patients had no elevated CRP values throughout their clinical courses and were discharged on hospital days 12, 12, and 15, respectively. The other patient, Case 7 described below, developed pneumonia during hospitalization.



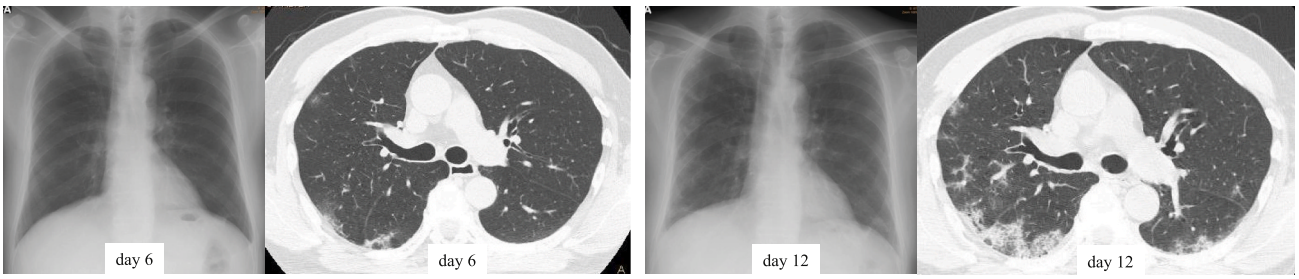
Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Hospital day							1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
PCR					(+)																				(+)			(-)			(-)		
BT (℃)	37.4	36.8	36.5	37.5	38.0	37.1	36.9	36.8	36.4	36.4	36.8	37.0	36.9	36.8	36.4	36.4	36.8	36.5	36.6	36.6	36.9	36.6	36.4	36.3	36.6	36.6	36.3	36.5	37.0	36.5	36.4	36.5	36.3
SpO_2 (%)							97	96	97	96	92	95	94	95	95	96	96	97	97	98	96	96	96	97	97	97	98	97	98	97	96	98	
CRP (mg/dL)							0.88	0.99		1.03				1.71			0.84			0.30					0.06						0.04		
Sore throat																																	
Rhinorrhea																																	
Cough																																	
Sputum																																	
Arthralgia, myalgia																																	
Dyspnea																																	
Dizziness																																	
Diarrhea																																	
Nausea, vomitting																																	
Headache																																	
Antibiotics							ABPC/SBT+CAM					CAM																							
Antivirals																																	
Oxygen therapy																																	
Other treatment																																	

Fig. 2. Clinical course and chest imaging of Case 1. Chest X-ray on day 7 showed patchy ground-glass opacities and consolidation in the right middle lung field, and CT showed consolidations and ground-glass opacities in the right upper lung. Chest CT on day 17 showed improvement of that shadow, but new lesions had developed.



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Hospital day				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
PCR		(+)																									(-)			
BT (℃)				36.1	38.2	38.7	38.2	39.1	39.1	37.5	37.9	37.4	36.9	38.1	38.8	38.5	38.3	37.1	37.0	36.8	36.5	36.4	36.5	36.6	36.2	36.5	36.6	36.8	36.4	36.3
SpO_2 (%)				98	98	97	99	95	94	93	98	97	97	98	97	98	97	97	96	97	97	97	97	96	97	98	96	97	99	98
CRP (mg/dL)				0.69			0.88			6.15				1.31		2.47		4.62		1.20				0.13						
Sore throat																														
Rhinorrhea																														
Cough																														
Sputum																														
Arthralgia, myalgia																														
Dyspnea																														
Dizziness																														
Diarrhea																														
Nausea, vomitting																														
Headache																														
Antibiotics					CTRX											ABPC/SBT														
Antivirals										Lopinavir/Ritonavir						Lopinavir/Ritonavir														
Oxygen therapy																														
Other treatment																IVIg														

Fig. 3. Clinical course and chest imaging of Case 2. Chest X-ray on day 4 showed no abnormal findings, and CT showed patchy ground-glass opacities. Shadows increased on day 10 and slightly improved on day 12.

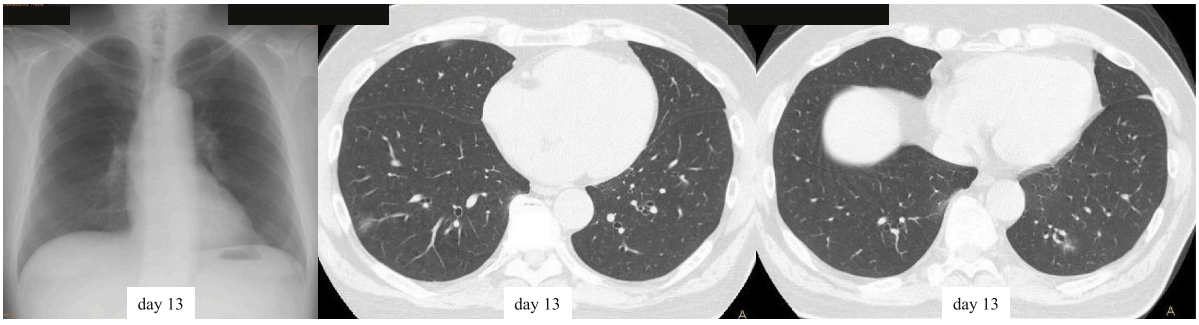


Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Hospital day						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25	27
PCR			(+)																	(+)			(-)			(+)		(-)				
BT (℃)	38.5					36.2	38.0	38.1	38.5	37.7	36.5	37.0	37.2	36.8	37.5	36.9	36.9	36.8	37.0	36.8	36.7	36.6	36.4	36.5	36.3	36.2	36.4	36.8	36.6	36.6	36.5	36.2
SpO_2 (%)						98	95	96	94	92	94	92	96	96	95	97	97	96	96	95	95	95	96	97	97	97	97	97	97	97	97	97
CRP (mg/dL)						4.95			9.25			5.57				1.02						0.09										
Sore throat																																
Rhinorrhea																																
Cough																																
Sputum																																
Arthralgia, myalgia																																
Dyspnea																																
Dizziness																																
Diarrhea																																
Nausea, vomitting																																
Headache																																
Abdominal pain																																
Antibiotics						CTRX+CAM																										
Antivirals												Lopinavir/Ritonavir																				
Oxygen therapy																																
Other treatment																																

Fig. 4. Clinical course and chest imaging of Case 3. Chest X-ray on day 6 showed no abnormal shadows, but CT showed patchy subpleural consolidation and ground-glass opacities. Pulmonary shadows had increased on day 12.

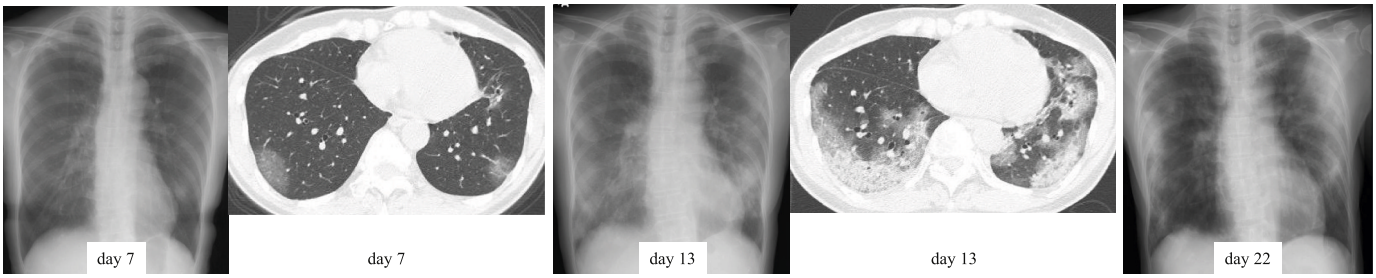
2.2. SARS-CoV-2 pneumonia case reports

Case 1. An 81-year-old woman had headache, dizziness, appetite loss, sore throat, and dry cough. The cough gradually improved, but arthralgia, myalgia, and appetite loss developed. PCR testing for SARS-CoV-2 on day 5 was positive. She was transferred to our hospital on day



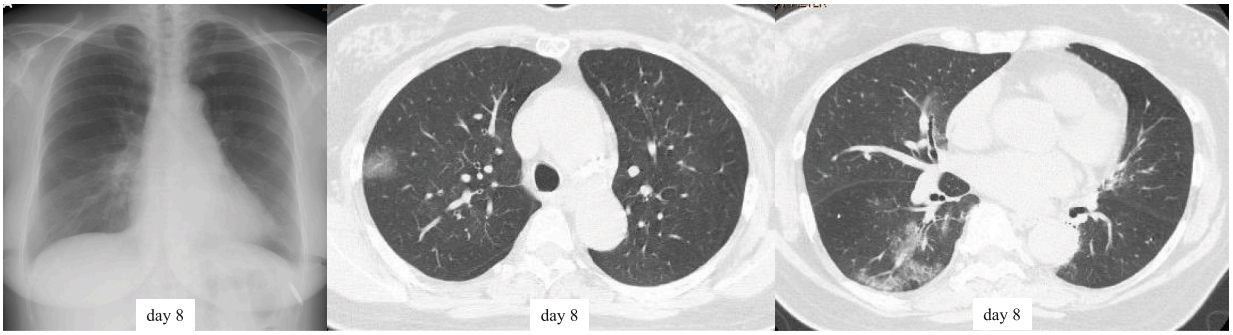
Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Hospital day													1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
PCR										(+)																				(-)			(+)		(-)	(-)		
BT (℃)			38.5										35.9	37.0	37.7	37.6	37.0	36.6	36.5	37.4	36.9	36.4	36.8	36.6	36.8	36.8	36.4	36.3	36.4	36.6	36.6	36.9	36.6	36.9	36.8	36.7	36.9	36.4
SpO_2 (%)													100	98	98	97	98	97	98	98	98	99	98	98	98	99	99	98	98	99	98	98	99	99	98	99	98	97
CRP (mg/dL)													0.1						0.2																			
Sore throat																																						
Rhinorrhea																																						
Cough																																						
Sputum																																						
Arthralgia, myalgia																																						
Dyspnea																																						
Dizziness																																						
Diarrhea																																						
Nausea, vomitting																																						
Headache																																						
Red eyes																																						
Antibiotics																																						
Antivirals																																						
Oxygen therapy																																						
Other treatment																																						

Fig. 5. Clinical course and chest imaging of Case 4. Chest X-ray on admission did not show any abnormal findings, but CT showed patchy ground-glass opacities.



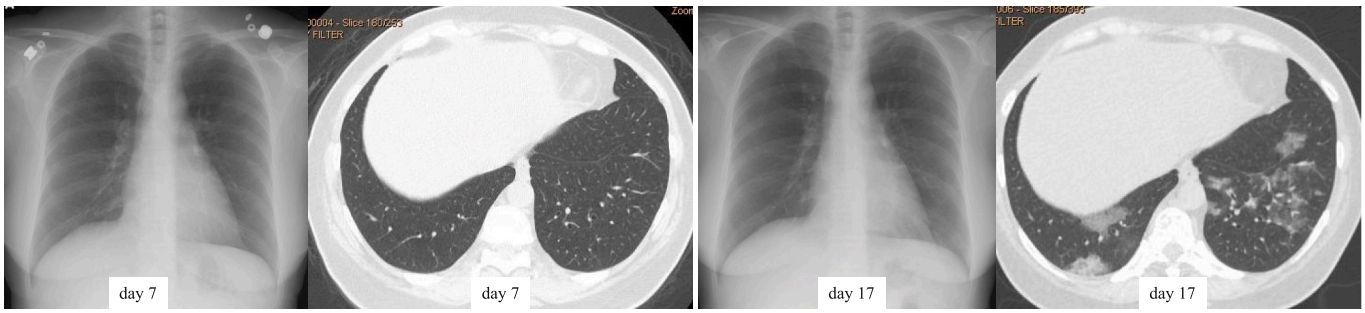
Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Hospital day							1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
PCR					(+)																												
BT (ºC)			37.8				38.3	37.8	39.4	38.6	38.6	38.6	38.2	38.4	38.5	38.1	38.3	38.0	37.2	36.9	37.4	36.8	37.0	36.5	36.7	36.9	36.7	36.8	36.7	36.5	36.7	36.5	36.5
SpO_2 (%)							96	96	97	94	92	90	91	96	97	94	95	97	95	96	98	97	98	98	99	99	100	97	99	98	97	96	98
CRP (mg/dL)							1.47			2.34			12.19			17.56	17.30	15.43		9.34		5.74		3.33			1.09			0.41			
Sore throat																																	
Rhinorrhea																																	
Cough																																	
Sputum																																	
Arthralgia, myalgia																																	
Dyspnea																																	
Dizziness																																	
Diarrhea																																	
Nausea, vomitting																																	
Headache																																	
Abdominal pain																																	
Antibiotics							CTRX+CAM																										
Antivirals													Lopinavir/Ritonavir																				
Oxygen therapy													2L/min			HFNC				5L/min	3L/min			1 L/min								
Other treatment															IVIg																		

Fig. 6. Clinical course and chest imaging of Case 5. Chest X-ray on day 7 showed patchy consolidation in the left lower lung field. CT showed subpleural ground-glass opacities. Pulmonary shadows increased on day 13 and then gradually improved on day 16 and 22.



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Hospital day								1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PCR					(+)														(-)	(+)			(-)		(-)			
BT (ºC)	37.1	38.1						36.8	36.6	36.6	36.9	36.5	36.9	36.8	37	36.7	36.6	37	36.8	36.8	36.8	36.8	36.6	36.2				
SpO_2 (%)								96	96	97	97	96	96	97	96	96	97	97	97	96	98	98	97	98	96	97	96	97
CRP (mg/dL)								2.11									0.09											
Sore throat																												
Rhinorrhea																												
Cough																												
Sputum																												
Arthralgia, myalgia																												
Dyspnea																												
Dizziness																												
Diarrhea																												
Nausea, vomitting																												
Headache																												
Antibiotics																												
Antivirals																												
Oxygen therapy																												
Other treatment																												

Fig. 7. Clinical course and chest imaging of Case 6. Chest X-ray showed ground-glass opacities in the right middle and lower lung fields. Chest CT showed patchy GGOs and consolidation.



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Hospital day								1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
PCR						(+)																											(-)		(-)					
BT (°C)					36.7	37.0	36.7	38.1	38.5	38.4	37.6	37.5	37.1	37.3	36.8	37.0	37.1	37.0	37.0	36.9	36.5	36.9	36.9	36.8	36.9	37.1	37.0	36.6	36.9	37.1	37.1	36.9	36.7	36.8	37.1	37.2	37.0	36.8
SpO_2 (%)								98	97	98	93	96	95	96	94	96	94	95	94	95	98	98	99	97	97	97	98	98	98	97	98	98	98	98	98	98	98	98
CRP (mg/dL)								0.09			0.17		1.22					2.35			0.38					0.09						0.06						
Sore throat																																						
Rhinorrhea																																						
Cough																																						
Sputum																																						
Arthralgia, myalgia																																						
Dyspnea																																						
Dizziness																																						
Diarrhea																																						
Nausea, vomitting																																						
Headache																																						
Antibiotics															ABPC/SBT+CAM				CAM																				
Antivirals																																						
Oxygen therapy																																						
Other treatment																																						

Fig. 8. Clinical course and chest imaging of Case 7. Chest X-ray and CT on day 7 showed no abnormal shadows, but pulmonary infiltration developed on day 17.

7. Her chest X-ray and CT showed right-sided patchy GGO and consolidation (Fig. 2). We started ampicillin/sulbactam plus clarithromycin. Her CRP increased to 1.71 mg/dL up to day 14. On day 17, respiratory symptoms and fatigue were improving, but she still had no appetite. We performed another CT scan, which showed improvement of the shadows on admission, but new shadows had developed. Her appetite loss gradually improved, and her CRP dropped to <0.3 mg/dL on day 20. She was discharged on day 33.

Case 2. A 66-year-old woman developed a 38 °C fever, cough, and arthralgia. Her cough improved spontaneously but relapsed, and sore throat and other symptoms appeared. PCR testing on day 2 was positive. She was transferred to our hospital on 4 day. Chest X-ray was normal, but CT showed bilateral GGOs (Fig. 3). We administered ceftriaxone plus clarithromycin, but her symptoms and respiratory condition worsened. Pulmonary shadows increased, and we started ritonavir/lopinavir on day 10. Pulmonary shadows increased until day 12 day with a CRP of 6.15 mg/dL and blood gas analysis under ambient air of pH 7.482, PaCO2 33.8 Torr, PaO2 68.8 Torr, and HCO3- 24.7 mmol/L but gradually improved thereafter. Her CRP decreased to 1.31 mg/dL on day 14.

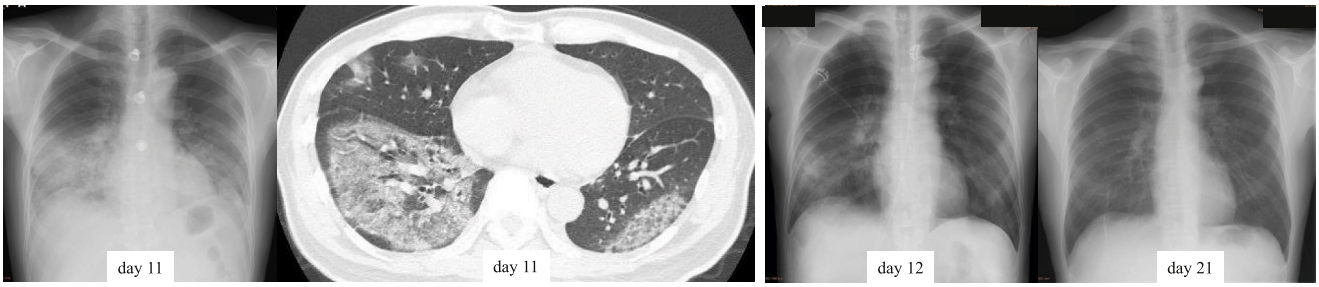
Case 3. A 69-year-old man developed fever and was transferred to our hospital on day 6 with fever, headache, sore throat, nasal discharge, diarrhea, arthralgia, dizziness, and sputum. PCR testing on day 3 was positive. Although his chest X-ray was normal, CT showed bilateral subpleural consolidation. GGOs were found in all lung lobes (Fig. 4). We started ceftriaxone plus clarithromycin. On day 12, blood gas analysis under ambient air showed pH 7.473, PaCO2 33.6 Torr, PaO2 70.0 Torr, HCO3- 24.1 mmol/L, elevated CRP of 5.57 mg/dL, and his chest X-ray had worsened. We began ritonavir/lopinavir, but pulmonary shadows continued to worsen until day 14 and then improved. His CRP improved to 1.02 mg/dL on day 16, and he remains in stable condition.

Case 4. A 70-year-old man developed fatigue, red eyes, and fever of 38.5 °C, followed by a cough that spontaneously improved. After positive PCR testing on day 10, he was transferred to our hospital. Admission chest X-ray was normal, but CT showed bilateral GGOs (Fig. 5). He remained stable during hospitalization and was discharged on day 38.

Case 5. A 69-year-old woman developed appetite loss, nausea, fever of 37.5–37.8 °C, cough, sputum, and diarrhea. PCR testing on day 5 was positive, and she was transferred to our hospital on day 7 (Fig. 6). Chest X-ray showed patchy consolidation in the left lower lung field. CT showed subpleural GGOs. Her dyspnea worsened, and blood gas analysis under ambient air on day 13 was pH 7.510, PaCO2 34.7 Torr, PaO2 58.8 Torr, and HCO3- 27.1 mmol/L. Chest X-ray showed increased pulmonary shadows (Fig. 6). We started ritonavir/lopinavir and intravenous immunoglobulin (IVIg) therapy on day 15 along with high-flow nasal cannula (HFNC) therapy. The pulmonary shadows on chest X-ray continued to worsen until day 15 and then gradually improved. Her CRP peaked at 17.56 mg/dL on day 16 and then decreased to 0.41 mg/dL on day 30.

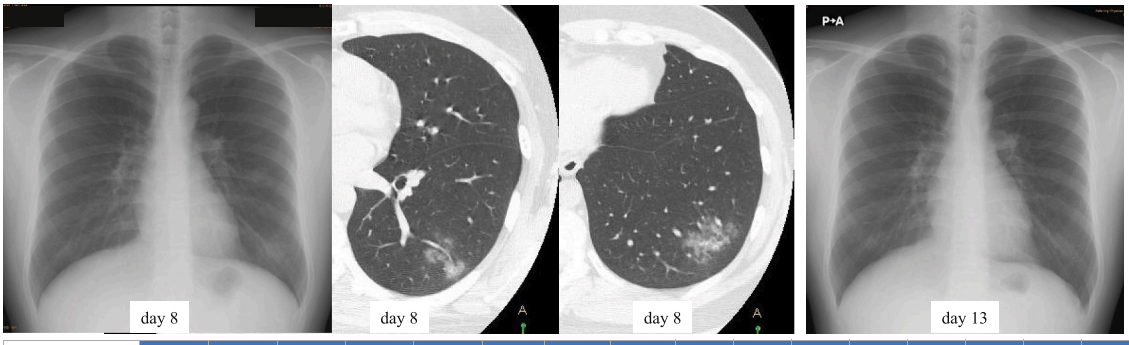
Case 6. A 64-year-old woman developed fever, cough, diarrhea, nausea, and appetite loss. Her PCR test on day 5 was positive, and she was transferred to our hospital on day 8. Her symptoms improved until admission to our hospital, where chest X-ray on admission showed patchy GGOs in right middle and lower lung fields. Chest CT showed GGOs (Fig. 7). Because she had no symptoms on admission, we followed her without antibiotics or antivirals. Her condition continued to be stable and she was discharged on day 28.

Case 7. A 54-year-old woman initially developed red eyes and then sore throat, dry cough, headache, and myalgia. Her PCR test on day 6 was positive, and she was transferred to our hospital on day 8. On admission, her chest X-ray and CT showed no abnormal shadows (Fig. 8), and we followed her without antibiotics and antivirals. Her appetite loss and cough continued after admission, and her CRP gradually increased. On day 17, although a chest X-ray appeared normal, CT showed subpleural consolidation and bilateral GGOs. We started ceftriaxone plus clarithromycin, and she became afebrile 3 days later. Her CRP gradually decreased and became negative, and she was discharged



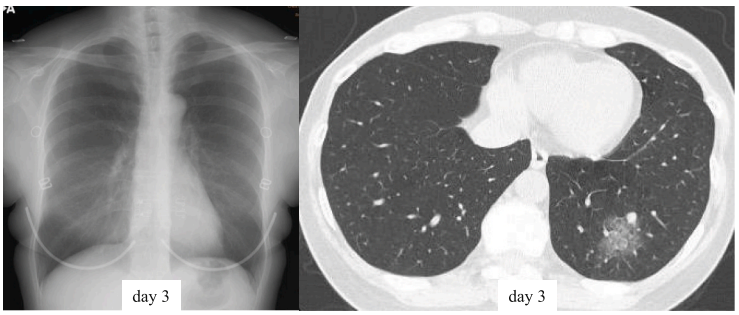
Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Hospital day											1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
PCR						(+)																					
BT (ºC)	36.7	36.9	37.6	37.4	37.3	38.4	37.9	37.9	37.8	37.0	36.5	36.6	37.1	37.4	36.7	36.9	36.8	36.5	36.6	36.6	36.5	36.5	36.6	36.5	36.5	36.4	36.7
SpO_2 (%)											93	95	95	93	99	97	97	98	95	98	97	97	98	97	97	97	97
CRP (mg/dL)											5.13				3.59			0.40			0.17			0.11			
Sore throat																											
Rhinorrhea																											
Cough																											
Sputum																											
Arthralgia, myalgia																											
Dyspnea																											
Dizziness																											
Diarrhea																											
Nausea, vomitting																											
Headache																											
Antibiotics											CAM																
Antivirals											Lopinavir/Ritonavir																
Oxygen therapy											3L/min				2L/min												
Other treatment											IVIg																

Fig. 9. Clinical course and chest imaging of Case 8. Broad bilateral consolidation and ground-glass opacities were found on day 11. On day 12, pulmonary shadows decreased and had improved remarkably on day 21.



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Hospital day								1	2	3	4	5	6	7	8	9	10	11	12	13
PCR					(+)											(-)			(-)	
BT (ºC)								36.5	36.4	36.7	37.0	36.7	36.9	36.9	36.9	36.3	36.4	36.7	36.5	36.9
SpO_2 (%)								97	98	98	99	98	100	97	99	99	98	98	100	99
CRP (mg/dL)								0.25					0.07						0.06	
Sore throat																				
Rhinorrhea																				
Cough																				
Sputum																				
Arthralgia, myalgia																				
Dyspnea																				
Dizziness																				
Diarrhea																				
Nausea, vomitting																				
Headache																				
Antibiotics								CTRX+CAM												
Antivirals																				
Oxygen therapy																				
Other treatment																				

Fig. 10. Clinical course and chest imaging of Case 9. Chest X-ray on day 8 showed patchy ground-glass opacities in the left middle and lower lung fields. CT showed patchy subpleural ground-glass opacities. Pulmonary shadows gradually improved on days 13 and 19.



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Hospital day			1	2	3	4	5	6	7	8	9	10	11	12	13	14
PCR	(+)										(-)			(-)		
BT (℃)	38.0	37.7	38.0	37.8	37.6	37.7	36.9	36.7	36.4	36.5	36.4	35.9	36.2	36.2	36.1	36.2
SpO_2 (%)			100	99	98	98	98	97	98	98	100	98	99	99	98	99
CRP (mg/dL)			0.20							0.14						
Sore throat																
Rhinorrhea																
Cough							■									
Sputum																
Arthralgia, myalgia					■											
Dyspnea		■														
Dizziness																
Diarrhea					■											
Nausea, vomitting				■												
Headache								■								
Antibiotics																
Antivirals																
Oxygen therapy																
Other treatment																

Fig. 11. Clinical course and chest imaging of Case 10. Chest X-ray on day 3 did not show abnormal shadows, but CT detected ground-glass opacities in the left lower lobe.

Table 1
Patient characteristics.

Case	Virus	Sex	Age (yrs)	Underlying pulmonary diseases	Underlying non-pulmonary diseases	Smoking status	Period from initial symptoms to diagnosis of pneumonia (days)	Severity on diagnosis of pneumonia
1	SARS-CoV-2	F	81	Asthma	HT, DM	No	7	Severe
2	SARS-CoV-2	F	66	No	Dyslipidemia	No	3	Moderate
3	SARS-CoV-2	M	69	COPD	DM, dyslipidemia	Current	5	Moderate
4	SARS-CoV-2	M	70	No	No	No	11	Moderate
5	SARS-CoV-2	F	69	No	No	No	6	Moderate
6	SARS-CoV-2	F	64	No	No	No	4	Moderate
7	SARS-CoV-2	F	54	Asthma	DM	No	17	Moderate
8	SARS-CoV-2	M	64	No	Gout	No	11	Moderate
9	SARS-CoV-2	M	26	No	No	No	8	Moderate
10	SARS-CoV-2	F	56	No	No	No	3	Moderate
11	SARS-CoV-2	F	65	No	No	No	4	Moderate
12	HCoV-229E	M	50	No	CKD	Current	29	Severe
13	HCoV-NL63	M	77	No	DM	Current	16	Severe
14	HCoV-OC43	M	74	Asthma, COPD	CHF	Current	9	Severe
15	HCoV-OC43	M	75	No	Af, HT	No	24	Severe
16	HCoV-HKU1	M	75	ILD	No	No	4	Severe

SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; HCoV = human coronavirus; F, female; M, male; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; HT = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; CHF = congestive heart failure; Af = atrial fibrillation.

Table 2
Symptoms during hospitalization.

Virus type	SARS-CoV-2	cHCoV
Sore throat	5 (45.5)	1 (20.0)
Rhinorrhea	2 (18.2)	0 (0)
Cough	11 (100)	4 (80.0)
Sputum	5 (45.5)	2 (40.0)
Arthralgia, myalgia	4 (36.4)	0 (0)
Dyspnea	2 (18.2)	4 (80.0)
Dizziness	2 (18.2)	0 (0)
Diarrhea	5 (45.5)	1 (20.0)
Nausea, vomiting	6 (54.5)	1 (20.0)
Fever	9 (81.8)	4 (80.0)
Headache	4 (36.4)	1 (20.0)
Body temperature	38.2 (36.5–39.0)	38.2 (37.8–40.2)

Data are expressed as number (%).
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; cHCoV = conventional human coronavirus.

on day 38.

Case 8. A 64-year-old man developed fever, cough, and sputum, and after a positive PCR test, he was transferred to our hospital. On admission, he was afebrile, but his SpO2 under ambient air was 93% and blood gases under ambient air showed hypoxemia. Chest X-ray showed bilateral consolidation mainly distributed in the bilateral lower lung fields. CT showed bilateral GGOs (Fig. 9). After admission, his SpO2 decreased to 89%, and we started IVIg, ritonavir/lopinavir, and clarithromycin. A chest X-ray the next day showed improvement. His SpO2 also improved, and on day 21, he was in stable condition, and laboratory testing showed a CRP of 0.06 mg/dL.

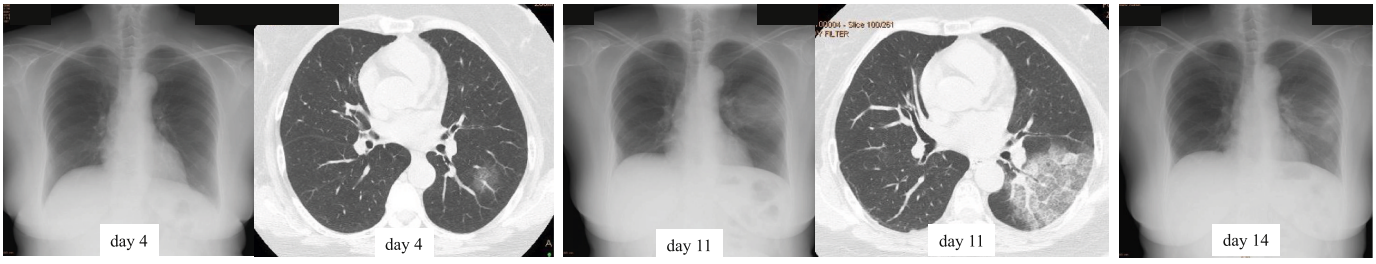
Case 9. A 26-year-old man developed cough and sputum. PCR testing was positive on day 5, and he was transferred to our hospital on day 8. Chest X-ray showed left-sided patchy GGOs, and CT showed patchy bilateral GGOs (Fig. 10). We started ceftriaxone plus clarithromycin, and his condition gradually improved. On day 19, he was in stable condition, and laboratory testing showed a CRP of 0.06 mg/dL. He was discharged on day 20.

Case 10. A-56-year-old woman developed a fever and dyspnea on the day following. PCR testing was positive, and she was transferred to our hospital on day 3. Because her symptoms, laboratory data, and radiological findings were mild with patchy GGOs detectable only by CT (Fig. 11), we did not administer antibiotics or antivirals, and she remained in stable condition during hospitalization. Her CRP was 0.14 mg/dL, and she was discharged on day 16.

Case 11. A 65-year-old woman developed sore throat and was transferred to our hospital for follow-up because COVID-21 was strongly suspected. She developed diarrhea, and her CRP remained slightly increased after admission. On day 11, her SpO2 decreased, and blood gas analysis under ambient air was pH 7.420, PaCO2 37.2 Torr, PaO2 64.8 Torr, and HCO3- 23.6 mmol/L. Chest X-ray showed left-sided consolidation. Chest CT showed consolidation and GGOs in the left lower lobe, and we started ritonavir/lopinavir, IVIg, and oxygen therapy. Her PCR test turned positive on day 12. Her symptoms and chest X-ray had improved on day 14.

2.3. SARS-CoV-2 versus cHCoV pneumonia

All pneumonia associated with SARS-CoV-2 was primary viral pneumonia. The SARS-CoV-2 pneumonia patients included 4 men and 7 women, whereas the cHCoV pneumonia patients comprised 5 men (Table 1). Three patients with SARS-CoV-2 pneumonia had underlying respiratory diseases, one with COPD plus asthma and two with asthma. Seven patients had underlying non-respiratory diseases. Only one patient smoked. The patients with cHCoV pneumonia included 3 smokers, 2 with underlying respiratory diseases (asthma, asthma and COPD), and 4 with underlying non-respiratory diseases (diabetes mellitus, congestive heart failure, atrial fibrillation, hypertension, and chronic kidney



Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Hospital day			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PCR	(-)		(-)									(+)								
BT (ºC)			37.6	37.6	37.7	37.3	36.8	37.3	36.6	37.1	36.5	36.2	36.7	36.9	37.0	36.8	36.3	36.5	36.5	36.3
SpO_2 (%)			98	98	98	97	97	98	95	94	93	98	96	98	96	97	97	98	98	98
CRP (mg/dL)				0.92		1.47		1.49			1.41			3.55				3.23		0.8
Sore throat																				
Rhinorrhea																				
Cough																				
Sputum																				
Arthralgia, myalgia																				
Dyspnea																				
Dizziness																				
Diarrhea																				
Nausea, vomitting																				
Headache																				
Antibiotics																				
Antivirals											Lopinavir/Ritonavir									
Oxygen therapy											1L/min									
Other treatment											IVIg									

Fig. 12. Clinical course and chest imaging of Case 11. Chest X-ray on day 4 showed no abnormal pulmonary shadows, but left-sided consolidation developed on day 11, which decreased on day 14. Chest CT on day 4 detected a patchy ground-glass opacity in the left lower lobe, which had progressed on day 11.

Table 3
Blood gas analysis on development of pneumonia.

Case	Condition	pH	$PaCO_2$ (Torr)	PaO_2 (Torr)	HCO_3^- (mmol/L)	Lactate (mmol/L)	SpO_2 (%)
1	Ambient air	7.419	39.2	62.1	24.8	0.79	96
2	Ambient air	7.407	38.8	92.9	23.9	1.52	98
3	Ambient air	7.404	32.9	84.3	20.1	2.63	98
4	Ambient air						100
5	Ambient air	7.468	38.6	78.5	27.3	0.92	96
6	Ambient air						100
7	Ambient air	7.385	51.7	60.7	30.2	1.08	98
8	Ambient air	7.44	31.6	64.8	21	1.45	93
9	Ambient air	7.36	45.1	86.8	26.3	1.77	96
10	Ambient air						100
11	Ambient air						98
12	FiO_2 0.28	7.372	27.5	47.1	26.7		82
13	Ambient air	7.456	30.6	54.8	21.1		88
14	Ambient air	7.504	29.4	50.5	22.6		86
15	FiO_2 0.36	7.45	41.8	54.2	28.4	0.93	78
16	FiO_2 0.44	7.452	34.7	67.1	23.7	3.76	96

FiO_2 was calculated as 4% increase with O_2 supplementation of 1 L/min; SpO_2 = O_2 saturation measured by pulse oximeter; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen in arterial blood, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood.

Table 4
Laboratory data on admission of patients with coronavirus pneumonia.

Test	SARS-CoV-2 (n = 11)	cHCoV (n = 5)
WBC,/mm^3	5100 (2400–7200)	8900 (4600–13600)
Neu,/mm^3	3800 (1600–5800)	7200 (3800–11900)
Lym,/mm^3	900 (600–1700)	600 (400–1500)
Mo,/mm^3	300 (200–600)	600 (100–1000)
Hb, g/dL	13.7 (12.2–15.5)	12.6 (10.8–14.2)
Plt,/mm^3	19.6 (14.8–31.3)	26.6 (14.0–31.8)
AST, IU/L	29 (17–39)	36 (16–48)
LDH, IU/L	180 (144–408)	312 (234–586)
CK, IU/L	82 (25–259)	51 (41–125)
BUN, mg/dL	12 (8–19)	16 (8–41)
Cre, mg/dL	0.61 (0.51–0.97)	0.82 (0.68–5.1)
CRP, mg/dL	0.92 (0.05–5.13)	9.2 (4.8–22.96)
PCT, ng/mL	0.045 (0.03–0.09)	0.143 (0.081–0.21)

Data are expressed as median (range). WBC = white blood cells; Neu = neutrophils; Lym = lymphocytes; Mo = monocytes; Hb = hemoglobin; Plt = platelets; AST = aspartate transferase; LDH = lactate dehydrogenase; CK = creatine kinase; BUN = blood urea nitrogen; Cre = creatinine; CRP = C-reactive protein; PCT = procalcitonin.

disease).

The 11 SARS-CoV-2 pneumonia patients were admitted from 3 to 8 days after initial symptoms onset, and 3 patients developed pneumonia >10 days from symptom onset. Five patients (45.5%) developed diarrhea, and 6 (54.5%) developed nausea and vomiting (Table 2). Overall, 7 of our 11 (63.6%) SARS-CoV-2 pneumonia patients had gastrointestinal symptoms, whereas only 1 of the 5 patients with cHCoV pneumonia developed gastrointestinal symptoms. The patients with SARS-CoV-2 pneumonia repeated the relapse of and recovery from their symptoms during their clinical courses (Figs. 2–12) (see Fig. 13).

Only one of the SARS-CoV-2 pneumonia patients was in severe condition on admission (Table 3), but 5 patients worsened during hospitalization, and one patient (Case 5) required HFNC therapy. Overall, 3 patients were classified as having severe disease. Contrastingly, all of the cHCoV pneumonia patients were in respiratory failure on admission. Elevated CRP values were present in the cHCoV pneumonia patients, but procalcitonin values were low in all patients (Table 4).

Chest X-ray and CT findings obtained when pneumonia developed are listed in Tables 5 and 6 and Fig. 13. Abnormal X-ray shadows were not detectable in 4 (36.3%) of the 11 SARS-CoV-2 pneumonia patients throughout their course, but abnormal shadows were found in the other patients on admission or during hospitalization. Chest X-ray findings worsened during days 6–16 from initial symptoms onset. Chest X-ray findings were worst on death in the non-surviving cHCoV pneumonia patient but worse at 3 weeks after onset in the other patients.

Five of the 11 SARS-CoV-2 pneumonia patients received antivirals (ritonavir/lopinavir) (Table 7), 4 because of worsening symptoms under antibiotics, and the other (Case 8) because of broad pulmonary shadows with hypoxemia on admission. In 3 patients, symptoms and chest X-ray findings continued to worsen for 3 days and then improved, whereas the other 2 patients improved the next day. Four of the 5 patients developed nausea, vomiting, and diarrhea after ritonavir/lopinavir administration, which improved after cessation of these agents. These appeared to be the only adverse effects. Three SARS-CoV-2 pneumonia patients required oxygen therapy, with one also requiring HFNC therapy. None of these patients died, and all had recovered by March 8, 2020.

3. Discussion

Human coronaviruses are positive-stranded, enveloped RNA viruses of the family *Coronaviridae*. Respiratory cHCoV infections occur more frequently in the winter and spring months, and during these times of peak viral activity, cHCoVs may be reasonably estimated to cause 15% of all adult colds. Four strains of non-SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) can cause pneumonia and other respiratory illnesses in healthy adults and the elderly. For example, cHCoV reportedly accounted for 5 (2.5%) of 198 pneumonias in Spain [4] and 6 (2.0%) of 304 pneumonias in New Zealand [5]. cHCoV may cause 2% of severe cases of pneumonia in patients admitted to the intensive care unit [6].

In a previous study, 2 (6.6%) of 30 patients infected with HCoV-OC43 developed pneumonia, whereas 19 (42.2%) of 45 patients with MERS-CoV infections developed pneumonia [7]. Among our 14 patients with COVID-19, 10 already had pneumonia on admission, and one developed it during hospitalization. This 78.6% (11/14) rate of pneumonia development indicates that patients with SARS-CoV-2 infections can easily develop pneumonia. Our patients were transferred to our institution because of respiratory symptoms and positive PCR results of SARS-CoV-2. They had not undergone chest X-rays until transfer to our hospital; thus, there might not be selection bias. Importantly, we performed CT on all patients without abnormal X-ray shadows and detected abnormal shadows in some patients. Had CT not been performed, these patients may not have been diagnosed as having pneumonia. Thus, CT was useful in detecting pneumonia in a high proportion of the symptomatic COVID-19 patients.

Complications of SARS-CoV-2 pneumonia include acute respiratory distress syndrome, acute renal injury, and septic shock, but our patients did not experience them [8]. Seven of our 11 (63.6%) patients with SARS-CoV-2 pneumonia had gastrointestinal symptoms, which seems

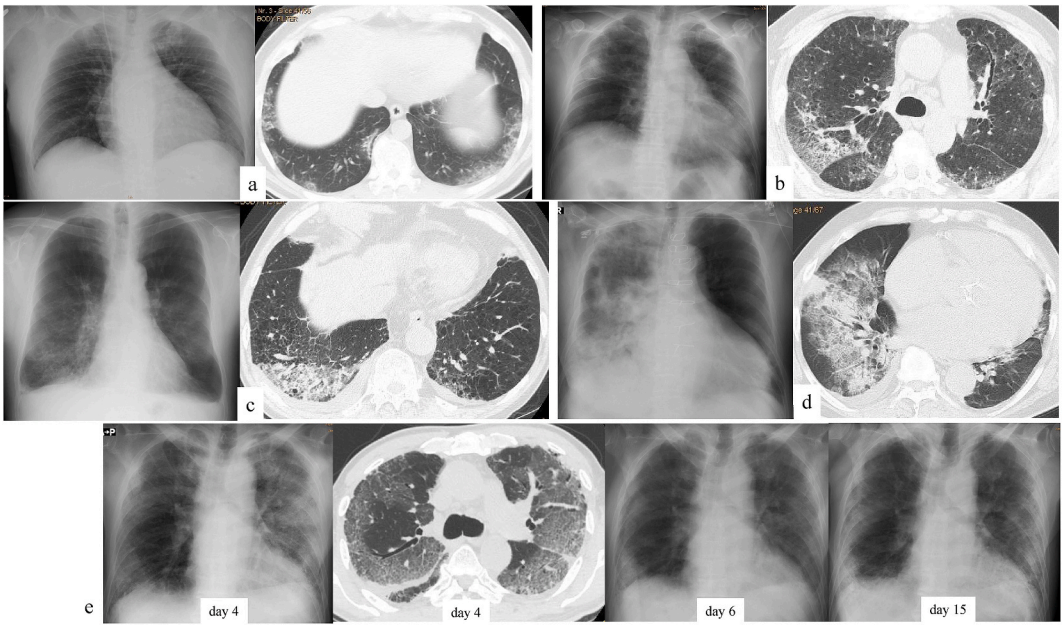


Fig. 13. Chest imaging of Case 12 (a), 13 (b), 14 (c), 15 (d), and 16 (e). a. Chest X-ray showed cardiomegaly, and CT showed subpleural ground-glass opacities. b. Chest X-ray showed consolidations predominantly in the outer zones. CT showed consolidation and ground-glass opacities in the bilateral lung fields. c. Chest X-ray and CT showed bilateral pleural effusion and subpleural consolidation. d. Chest X-ray showed right-sided consolidation with cardiomegaly. Chest CT showed consolidation and ground-glass opacities in the right lower lobe and right-sided pleural effusion. e. Chest X-ray and CT on day 4 showed bilateral ground-glass opacities and consolidation. Pulmonary shadows slightly improved on day 6 but worsened on day 15.

Table 5
Chest X-ray findings of patients with coronavirus pneumonia.

	SARS-CoV-2 (n = 11)	cHCoV(n = 5)
Consolidation	3 (27.3)	3 (60)
Patchy	2 (18.2)	2 (40)
Broad	1 (9.1)	1 [20]
GGO	4 (36.3)	5 (100)
Patchy	3 (27.3)	2 (40)
Broad	1 (9.1)	3 (60)
Bilateral shadows	1 (9.1)	4 (80)
Distribution of pulmonary shadows		
RULF	0	4 (80)
RMLF	3 (27.3)	3 (60)
RLLF	2 (18.2)	5 (100)
LULF	3 (27.3)	3 (60)
LMLF	2 (18.2)	2 (40)
LLLF	4 (36.3)	4 (80)
Pleural effusion	0	2 (40)

Data are expressed as number (%). SARS-CoV-2 = severe respiratory syndrome coronavirus-2; cHCoV = conventional human coronavirus; GGO = ground-glass opacity; RULF = right upper lung field; RMLF = right middle lung field; RLLF = right lower lung field; LULF = left upper lung field; LMLF = left middle lung field; LLLF = left lower lung field.

Table 6
CT findings on diagnosis of pneumonia.

Finding	SARS-CoV-2 (n = 11)	cHCoV (n = 5)
Consolidation	3 (27.3)	5 (100)
Bilateral	1 (9.0)	2 (40)
Ground-glass opacities	11 (100)	5 (100)
Bilateral	8 (72.7)	5 (100)
Subpleural	8 (72.7)	5 (100)
Along with bronchovascular bundles	11 (100)	3 (60)
Halo sign	2 (18.2)	3 (60)
Diffuse bronchial wall thickening	2 (18.2)	2 (40)
Centrilobular nodules	3 (27.3)	1 [20]
Pleural effusion	3 (27.3)	4 (80)
Hilar or mediastinal lymphadenopathy	0 (0)	2 (40)

Data are expressed as number (%). SARS-CoV-2 = severe respiratory syndrome coronavirus-2; cHCoV = conventional human coronavirus.

high when compared with the frequency reported elsewhere (8.0%) [9].

One patient in our study initially showed negative PCR results that later became positive. Sensitivity of the PCR test for SARS-CoV-2 is reported to be 30–60%.10 We performed follow-up PCR testing for this patient because she had close contact with COVID-19 and had gastrointestinal symptoms. Similar findings were reported previously [10].

How can we predict the development of pneumonia in SARS-CoV-2-infected patients? The identified predictive factors for pneumonia development in patients infected with MERS-CoV included age ≥45 years, fever ≥37.5 °C, thrombocytopenia, CRP ≥2 mg/dL, and threshold cycle value of PCR <28.5. With two or more predictive factors for pneumonia development, 100% of patients develop pneumonia [7]. In our SARS-CoV-2-infected patients, those with prolonged fever or elevated CRP value already had or subsequently developed pneumonia. Changes in the CRP value corresponded well with the development of pneumonia and changes in X-ray findings (improvement or worsening), indicating their usefulness.

Abnormal shadows were not detected on initial chest X-ray in 5 of our 11 patients with SARS-CoV-2 pneumonia. X-ray shadows may not be detectable or are unilateral in the early phase 8. X-ray findings worsened from 6 to 14 days after onset. In a previous study of CT scanning separated by a 4-day interval, maximum lung involvement peaked at approximately 10 days from initial symptoms onset [11], as in our experience.

Although the frequency of these findings differ when CT was performed, characteristic CT findings in SARS-CoV-2 pneumonia are reported to be bilateral GGOs [12–14]. Our SARS-CoV-2 pneumonia patients frequently showed bilateral and peripheral distribution of GGOs and relatively little consolidation compared with GGOs, as in previous reports [13]. Pulmonary shadows found on admission in Case 1 improved, but other shadows developed elsewhere, indicating a wandering course. Wandering shadows of short duration have been reported previously in patients with SARS-CoV-2 pneumonia [11].

We administered ritonavir/lopinavir to 5 of the 11 SARS-CoV-2

Table 7
Treatment during hospitalization.

Case	Treatment	Corticosteroids	Others	Outcome
1	ABTs	No	No	Recovered and discharged
2	Antivirals and IVIg because of worsening under ABTs	No	No	Recovered
3	Antivirals because of worsening under ABTs	No	No	Recovered
4	No drugs	No	No	Recovered and discharged
5	Antivirals and IVIg because of worsening under ABTs	No	Oxygen therapy, followed by HFNC	Recovered
6	No drugs	No	No	Recovered and discharged
7	ABTs	No	No	Recovered and discharged
8	Simultaneous start of ABTs and antivirals after admission because of respiratory failure	No	Oxygen therapy	Recovered
9	ABTs	No	No	Recovered and discharged
10	No drugs	No	No	Recovered and discharged
11	Antivirals and IVIg because of worsening during antibiotics	No	Oxygen therapy	Recovered
12	ABTs	No	Oxygen therapy	Recovered and discharged
13	ABTs	mPSL 1 g daily for 3 days followed by PSL 40 mg daily, tapering, because of worsening under ABTs	Oxygen therapy followed by HFNC	Recovered and discharged
14	ABTs	PSL 20 mg daily because of worsening under ABTs	Oxygen therapy	Recovered and discharged
15	ABTs	mPSL 1 g daily for 3 days followed by PSL 40 mg daily, tapering, because of worsening under ABTs	Oxygen therapy followed by HFNC	Recovered and discharged
16	ABTs	mPSL 1 g daily for 3 days followed by PSL 40 mg daily, tapering, simultaneous administration with ABTs	Oxygen therapy followed by HFNC	Death

ABTs = antibiotics; IVIg = intravenous immunoglobulins; HFNC = high-flow nasal cannula therapy; PSL = prednisolone; mPSL = , methylprednisolone.

pneumonia patients, and chest X-ray findings gradually began to improve 3 days after the initiation of these agents in 3 patients. Although the efficacy of these antivirals remains unclear [15], they appeared to us to be effective. However, 6 of the 11 patients with stable subjective feelings, respiratory conditions, and chest X-ray findings improved without these agents. Further studies need to clarify the characteristics of the patients who require such therapy.

The cHCoV pneumonia patients had acute progressive interstitial lung diseases and received corticosteroids rather than antiviral therapy. The efficacy of corticosteroids for viral pneumonia is controversial. One (20%) of 5 patients with primary cHCoV pneumonia died. Mortality rates of pneumonia due to cHCoV have not been fully investigated. Among 10 Hong Kong patients with pneumonia due to HoV-HKU1, 2 (20.0%) died [16], whereas none of 9 patients with pneumonia due to HCoV-NL63 died [17]. In Spain, none of 5 patients with coronavirus-229E or OC43 died [5]. The mortality rates of pneumonia due to SARS-CoV and MERS-CoV are reported to be 9.6% and 34.5%, respectively [18]. Mortality rates of pneumonia due to SARS-CoV-2 were initially reported to be 15% [19] and 11% [8], whereas another study reported a rate of 4.3% [20]. None of our patients died, but we treated only 11 patients. Recently, the mortality rate of SARS-CoV-2 infections (COVID-19) was reported as 2% by WHO, but the rate may include patients with other than pneumonia. A previous study suggested that the true number of exposed cases in Wuhan may be vastly underestimated. The focus on the thousands of cases might have caused mild or asymptomatic courses possibly accounting for the bulk of the SARS-CoV-2 infections to go largely unrecognized [21]. Exact numbers of subclinical, respiratory tract, and gastrointestinal infections, and pneumonias will need to be investigated to determine an accurate mortality rate from SARS-CoV-2 infections.

Elevated CRP levels and underlying diseases were reported as prognostic factors of SARS [22]. Abnormal coagulation parameters, age ($\geq$60 years), smoking history, body temperature on admission ($\geq$37.3 °C), respiratory failure, albumin (4.0 g/dL), and elevated CRP value (>8.2 mg/dL) are reported to be associated with its progression or prognosis [23,24], but further studies are needed.

This study has several limitations. We found a high prevalence of pneumonia in the SARS-CoV-2-infected patients. Abnormal CT shadows in some patients could be found only by CT, which led to a diagnosis of pneumonia. Accordingly, the high frequency of pneumonia may be due to the high use of CT.

In conclusion, the patients with COVID-19 easily developed gastrointestinal symptoms and pneumonia, which could be detected only by CT. Three (27%) patients developed pneumonia 10 or more days after initial symptoms onset. All pneumonia associated with SARS-CoV-2 was primary viral pneumonia. We administered ritonavir/lopinavir to 5 patients with SARS-CoV-2 pneumonia when their condition worsened and hypoxemia ensued, with apparent good effect. We report this result to further the accumulation of treatment results following the use of antiviral agents. Future problems to resolve include whether antiviral agents administered in cases of mild or moderate severity can reduce the number of severe cases, and whether antivirals administered in severe cases can reduce mortality. Future studies should also clarify which patients will require CT as the rates of COVID-19 increase.

Declaration of competing interest

Takashi Ishiguro, Kenji Takano, Naho Kagiyama, Chiaki Hosoda, Yoichi Kobayashi, Yotaro Takaku, Naomi Takata, Miyuki Ueda, Yasuhiro Morimoto, Keisuke Kasuga, Ryota Ozawa, Taisuke Isono, Takashi Nishida, Eriko Kawate, Yasuhito Kobayashi, Yoshihiko Shimizu, Kazuyoshi Kurashima, Tsutomu Yanagisawa, and Noboru Takayanagi declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101207.

Author contributions

T. I. is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. K. T. N. K. C. H. Yo. K. Y. T. Y. M. Ke. K. R. O. T. I. T. N. E. K. Ya. K. Y. S. Ka. K. T. Y. and No. T. aggregated the data, created the figures, and helped draft the discussion of the manuscript. Y. K. performed PCR testing. Na. T. and T. K. reviewed the computed tomography findings.

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