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.

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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
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.
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.

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.
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 6.

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.

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.
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.

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.
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 day 4. 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.
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.

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.
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                            | A, 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; A, atrial fibrillation.
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 disease).
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15 patients with SARS-CoV-2 developed pneumonia, whereas only 1 of the 5 patients with cHCoV pneumonia did not experience them [8]. Seven of our 11 (63.6%) patients with SARS-CoV-2 pneumonia had gastrointestinal symptoms, whereas only 1 of the 5 patients with cHCoV pneumonia developed gastrointestinal symptoms. The patients with SARS-CoV-2 may not have been diagnosed as having pneumonia. Thus, CT was useful in detecting pneumonia in a high proportion of the symptomatic patients who may not have been diagnosed as having pneumonia. 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 [3]. Seven of our 11 (63.6%) patients with SARS-CoV-2 pneumonia had gastrointestinal symptoms, which seems to

Table 3

| Case | Condition | pH | PaCO₂ (Torr) | PaO₂ (Torr) | HCO₃⁻ (mmol/L) | Lactate (mmol/L) | SpO₂ (%) |
|------|-----------|----|-------------|-------------|----------------|-----------------|----------|
| 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 | 7.404 | 32.9 | 84.3 | 20.1 | 2.63 | 98 |
| 5    | Ambient air | 7.468 | 38.6 | 78.5 | 27.3 | 0.92 | 96 |
| 6    | Ambient air | 7.385 | 51.7 | 60.7 | 30.2 | 1.08 | 98 |
| 7    | Ambient air | 7.44 | 31.6 | 64.8 | 21 | 1.45 | 93 |
| 8    | Ambient air | 7.36 | 45.1 | 86.8 | 26.3 | 1.77 | 96 |
| 9    | Ambient air | 7.36 | 45.1 | 86.8 | 26.3 | 1.77 | 96 |
| 10   | Ambient air | 7.36 | 45.1 | 86.8 | 26.3 | 1.77 | 96 |
| 11   | Ambient air | 7.36 | 45.1 | 86.8 | 26.3 | 1.77 | 96 |
| 12   |FiO₂ 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   |FiO₂ 0.36 | 7.45 | 41.8 | 54.2 | 28.4 | 92 | 78 |
| 16   |FiO₂ 0.44 | 7.452 | 34.7 | 67.1 | 23.7 | 3.76 | 96 |

FiO₂ was calculated as 4% increase with O₂ supplementation of 1 L/min; SpO₂ = O₂ saturation measured by pulse oximeter; FiO₂ = fraction of inspired oxygen; PaCO₂ = partial pressure of carbon dioxide in arterial blood, PaO₂ = partial pressure of oxygen in arterial blood.

| Complications of SARS-CoV-2 pneumonia |
|-------------------------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
| Acute respiratory distress syndrome | x | x | x | x |
| Acute renal injury | x | x | x | x |
| Septic shock | x | x | x | x |

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

Table 4

| Test | SARS-CoV-2 (n = 13) | chCoV (n = 5) |
|------|---------------------|--------------|
| WBC/mm³ | 5100 (2400-7200) | 8900 (4600-13600) |
| Neut/mm³ | 3800 (1600-5800) | 7200 (3800-11900) |
| Lym/mm³ | 900 (600-1700) | 600 (400-1500) |
| Mø/mm³ | 300 (200-600) | 600 (100-1000) |
| Hb/µg/dl | 13.7 (12.2-15.5) | 12.6 (10.8-14.2) |
| Pr/µm3 | 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) |

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.

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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. 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 patients. 

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Table 5

|                      | 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)            | 6 (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

|                      | 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.
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 eCoV 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 (≥60 years), smoking history, body temperature on admission (>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 under antiviral therapy. 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.

| 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              | No     | 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, tapering, 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.

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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. N. E. Ka. 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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References

[1] T. Ishiguro, N. Takayanagi, S. Yamaguchi, H. Yamakawa, K. Nakamoto, Y. Takaku, Y. Miyahara, N. Kagiya, K. Kurashima, T. Yanagisawa, Y. Sugita, Etiology and factors contributing to severity and mortality of community-acquired pneumonia, Intern. Med. 52 (3) (2013) 317–324.
[2] T. Ishiguro, Y. Kobayashi, R. Uozumi, N. Takata, Y. Takaku, N. Kagiyama, T. Kanacachi, Y. Shimizu, N. Takayanagi, Viral pneumonia requiring differentiation from acute and progressive diffuse lung diseases, Intern. Med. 58 (24) (2019) 3509–3516.
[3] Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology. 2020: 200463, https://doi.org/10.1148/radiol.2020200463 [Epub ahead of print].
[4] L.C. Jennings, T.P. Anderson, K.A. Beynon, A. Chua, R.T. Laing, A.M. Werno, S. Angeles Marcos, M. Camps, T. Pumarola, T. Pumarola, J. Antonio Martinez, F. Pan, T. Ye, P. Sun, G. Gui, B. Liang, L. Di, D. Zheng, J. Wang, R.L. Hesketh, L. Yang, C. Zheng, Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia, Radiology (2020) 200370, https://doi.org/10.1148/radiol.2020200370 [Epub ahead of print].
[5] A. Bernheim, X. Mei, M. Huang, Y. Z.A. Fayad, N. Zhang, K. Diao, B. Lin, X. Zha, K. Li, S. Li, H. Shan, A. Jacobi, M. Chung, Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection, Radiology (2020) 200463, https://doi.org/10.1148/radiol.2020200463 [Epub ahead of print].
[6] J.Y. Jin, L. Cai, Z.S. Cheng, H. Cheng, T. Deng S, Y.P. Fan, T.D. Fang, D.J. Huang, L.Q.6 Huang 7, Q.1 Huang, Y.2 Han, B.R Hui, F.S Hui, B.H I Li, S. Y, R.9 Li, K.10 Liang, L.K.2 Lin, L.S.1 Liu, J.S Ma, L.L. Li, M.Z.8 Peng, Y.9. Pan, Z. Y.11 Pan, X.O.5 Ren, H.M.12 Sun, Y.3.13 Yang, W.Y.1 Wang, H.I.2 Wu, C.Ji3 D. F.4 Wu, J.14 Xia, Y.10 Xiong, H.B.15 Xu, M.16 Yao, Y.2.F. Yuan, T.S.17 Ye, X. C.15 Zhang, Y.W.17 Zhang, Y.G.2 Zhang, H.M.6 Zhang 7, Y.14 Zhao, M.J.1 Zhao, ZI H15, Seng, XT18,19, wang Y20,21, wang X22,23.; , for the zhongnans hospital of wuhan university novel coronavirus management and research team, evidence-based medicine chapter of China international exchange and promotion association for medical and Health care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version), Mil Med Res 7 (1) (2020) 4.
[7] A. Bernheim, X. Mei, M. Huang, Y. Z.A. Fayad, N. Zhang, K. Diao, B. Lin, X. Zha, K. Li, S. Li, H. Shan, A. Jacobi, M. Chung, Chest CT findings in coronavirus disease-19 (COVID-19): a perspective from China. Radiology. 2020: 200490, doi:10.1148/radiol.2020200490. [Epub ahead of print].
[8] A. Young, S. T. Chambers, D. R. Murdoch, Incidence and characteristics of viral respiratory infections, medRxiv (2020), https://doi.org/10.1101/2020.02.11.20021493 .
[9] F. Pan, T. Ye, P. Sun, G. Gui, B. Liang, L. Di, D. Zheng, J. Wang, R.L. Hesketh, L. Yang, C. Zheng, Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia, Radiology (2020) 200370, https://doi.org/10.1148/radiol.2020200370 [Epub ahead of print].
[10] J.P. Kane, Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist, Radiology 295 (1) (2020) 16–17, https://doi.org/10.1148/radiol.2020200241 .