Tocilizumab for treating severe COVID-19 pneumonia refractory to combined hydroxychloroquine, lopinavir plus ritonavir and favipiravir: case series

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Abstract

Three patients with COVID-19 pneumonia received treatment with hydroxychloroquine combined with lopinavir plus ritonavir and favipiravir. Two patients early diagnosed with COVID-19 pneumonia received tocilizumab at severe pneumonia diagnosed and survived. The third patient was late diagnosed and received tocilizumab when the disease progressed to ARDS, and passed away.

Key Clinical Message

Early diagnosis and treatment of COVID-19 pneumonia, as well as timely treatment of severe pneumonia with tocilizumab are important for the survival of patients, as they may prevent cytokine storms' development.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported as the cause of bilateral interstitial pneumonia in Wuhan, Hubei province, China, in January 2020.[1] COVID-19 has spread rapidly worldwide due to being highly contagious. In March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic.[2,3]

Previous reports have shown common symptoms among patients with COVID-19 including fever (89%), dry cough (68%), fatigue (38%), and dyspnoea (19%).[4] Most patients with COVID-19 (84%) have mild disease that spontaneously recovers, and the rest (16%) develop severe disease.[4] The most common manifestation of these patients is pneumonia, which may rapidly progress to severe pneumonia and then to acute respiratory distress syndrome (ARDS) and/or organs dysfunction. This is due to an excessive host immune response by hyperactivation of cytotoxic T-cells and humoral immune response, particularly of interleukin (IL)-6, which plays an important role as a primary critical mediator for the development of cytokine storms, leading to respiratory failure, shock, and organ dysfunction.[4-6] A systematic review indicated that an anti-IL-6 receptor antibody (IL-6 receptor antagonist), namely tocilizumab, might benefit patients with severe disease, although data were limited.[7] However, early recognition of SARS-CoV-2 infection, as well as severe disease, and the timely treatment of patients with COVID-19 are important for the patients' survival, in order to prevent the occurrence of cytokine storms.[6,8]

Herein, we report three patients with confirmed SARS-CoV-2 infection who developed severe pneumonia that was refractory to treatment combination of hydroxychloroquine, lopinavir plus ritonavir and favipiravir. Tocilizumab was then administered, and disease severity was monitored using IL-6 and high sensitivity C-reactive protein (hs-CRP) levels.

CASE REPORTS

Case 1

A 58-year-old Thai man with chronic medical illness of hypertension, hyperlipidaemia, and coronary artery disease presented to the emergency department with symptoms of fever with chills, productive cough with white phlegm, sneezing, sore throat, and myalgia on March 27, 2020 (Table 1). His recent medications included manidipine (10 mg once daily, orally), atenolol (25 mg once daily, orally), rosuvastatin (20 mg once daily, orally), clopidogrel (75 mg once daily, orally), and aspirin (81 mg once daily, orally). He was a healthcare worker who had been in contact with a patient with confirmed SARS-CoV-2 infection on March 11, 2020 (Table 1), and had not attended work thereafter. On March 24, 2020 (day 14 after exposure), both samples of nasopharyngeal swab and oropharyngeal swab showed undetectable levels of SARS-CoV-2 RNA using real-time reverse transcription polymerase chain reaction (RT-PCR), and the patient had no symptoms.

On March 25 (day 15 after exposure), he had fever with chills, productive cough with white phlegm, sneezing, sore throat, and myalgia. The patient received treatment with oseltamivir (150 mg twice daily, orally) and azithromycin (500 mg once daily, orally), but the symptoms did not improve.

On March 27 (day 3 of illness), physical examination showed a body weight of 70 kg, height of 175 cm, body mass index of 22.8 kg/m^2, body temperature of 37.9 ^{o}C, heart rate of 90 beats/min, blood pressure of 136/85 mmHg, respiratory rate of 20 breaths/min, and arterial oxygen saturation (SpO_2) of 97% at room air (Table 1). Chest radiograph was normal, but chest computed tomography (CT) showed ground glass infiltration at the posterior segment of the left lower lobe by air bronchogram (Figure 1A). RT-PCR assay showed detectable levels of SARS-CoV-2 RNA at the region of ORF1ab/RdRp, E and N gene, in both samples of nasopharyngeal swab and throat swab. Laboratory findings showed lymphopenia (419 cells/mm^3). The patient was admitted to the negative pressure isolation ward and received treatment with hydroxychloroquine (400 mg every 12 hours for 1 day, then 200 mg every 12 hours, orally), darunavir (800 mg once daily, orally) and ritonavir (100 mg once daily, orally) as antiviral treatment, starting on March 28 (day 4 of illness). Azithromycin (500 mg once daily, orally) was given as an anti-microbial and anti-inflammatory agent (Table 1).

On March 30 (day 6 of illness), the patient developed symptoms of fatigue, watery diarrhoea, shortness of breath, and hypoxemia (SpO_2 92% at room air; Table 1). Chest radiograph on March 29, 2020 (day 5 of illness), showed progression of interstitial infiltration in the right middle and left lower lung zone (Figure 1B). Darunavir and ritonavir were then stopped, and lopinavir plus ritonavir (400/100 mg every 12 hours, orally) combined with favipiravir (1600 mg every 12 hours for 1 day, then 600 mg every 12 hours, orally) were prescribed as antiviral treatment. On March 31 (day 7 of illness), the patient had symptoms of fever, fatigue, anorexia, watery diarrhoea, and shortness of breath (Table 1). On April 2 (day 9 of illness), chest radiograph showed slightly increased interstitial infiltration of the right middle and left lower lung zone and new interstitial infiltration in the left upper lung zone.

On April 4 (day 11 of illness) (Table 1), the patient still had fever with productive cough, fatigue, anorexia, watery diarrhoea, shortness of breath, and hypoxemia (SpO_2 88% at room air). He was then transferred to the intensive care unit (ICU) with negative pressure isolation. Chest radiograph showed new alveolar infiltration at the right upper lung zone and increased alveolar infiltration in the right middle, left upper, and left lower lung zone (Figure 1C). Laboratory findings showed lymphopenia (408 cells/mm^3), increased hs-CRP (164.7 mg/L), increased levels of IL-6 (46.6 pg/mL), and increased levels of lactate dehydrogenase (LDH) (409 U/L). Tocilizumab (8 mg/kg/dose intravenous drip for 90 min with repeated dose in the next 12 h) was administered due to progression of hypoxemia and increased lung infiltration. The patient also

received supplement oxygen of 5 L/min via a nasal cannula in the prone position to keep SpO_2 >94%.

On April 5 (day 12 of illness) (Table 1), the IL-6 levels prior to receiving the second dose of tocilizumab markedly increased to 784.0 pg/mL. The patient's symptoms improved, with no fever, decreased cough, decreased shortness of breath, and increased SpO_2 (91% at room air). Laboratory findings showed lymphopenia (351 cells/mm^3), decreased hs-CRP levels (155.8 mg/L), and mildly elevated alanine aminotransferase (ALT) levels (41 U/L). Chest radiograph showed slightly decreased infiltration in both upper lung zones, but infiltration in both lower lung zones was unchanged. On April 6 (day 13 of illness) (Table 1), the symptoms gradually improved. Chest radiograph showed decreased lung infiltration, and laboratory findings showed lymphopenia (289 cells/mm^3) and markedly decreased levels of hs-CRP (63.1 mg/L).

On April 7 (day 14 of illness) (Table 1), laboratory findings showed increased absolute lymphocyte count (ALC; 758 cells/mm^3), decreased hs-CRP levels (31.6 mg/L), and mildly elevated ALT levels (56 U/L). Chest radiograph showed slightly decreased infiltration in both upper and lower lung zones on Apr 8 (day 15 of illness), compared to that in the prior chest radiograph, and markedly decreased infiltration on April 14 (day 21 of illness). The radiograph was normal on April 23 (day 30 of illness) (Figure 1D). However, both samples of nasopharyngeal swab and oropharyngeal swab still showed detectable levels of SARS-CoV-2 RNA using RT-PCR on May 2 (day 37 of illness), although the patient had no symptoms. The patient received hydroxychloroquine, lopinavir plus ritonavir and favipiravir for 10 days combined with azithromycin for 5 days.

Case 2

A 34-year-old Thai female presented to an acute respiratory infection clinic on April 11, 2020, with symptoms of fever (36.2ºC-38.6ºC) and sore throat. Physical examination revealed enlargement of both tonsils with exudate. She was diagnosed with acute exudative tonsillitis and received treatment with amoxicillin plus clavulanate (1 g every 12 hours, orally). She was a healthcare worker and had had contact with a patient with confirmed SARS-CoV-2 infection on March 26, 2020, and thereafter did not attend work. On April 8, 2020 (day 14 after exposure), both samples of nasopharyngeal swab and throat swab showed undetectable levels of SARS-CoV-2 RNA, and the patient had no symptoms. Her symptoms started on April 11 (day 17 after exposure), and both samples of nasopharyngeal swab and oropharyngeal swab were retested for SARS-CoV-2 RNA. The results showed detectable SARS-CoV-2 RNA levels at the region of ORF1ab, N gene, NS-1, and NS-2 in both samples (Table 2).

On April 12 (day 2 of illness) (Table 2), the patient had fever, dry cough, sore throat, myalgia, and fatigue. On physical examinations, body weight was 74.6 kg, height 160 cm, body mass index 29.1 kg/m^2, body temperature 37.0 ºC, heart rate 106 beats/min with regular rate and rhythm, blood pressure 120/80 mmHg, respiratory rate 18 breaths/min, and SpO_2 96% at room air. Both tonsils were still enlarged with exudate. Chest radiograph showed minimal interstitial infiltration in the left lower lung zone (Figure 2A), and chest CT scan without contrast showed patchy ground glass with overlying consolidation opacity and interlobar septal thickening at the inferior lingular segment of the left upper lobe (Figure 2B). Laboratory findings showed ALC of 1592 cells/mm^3.

The patient was admitted to the negative pressure isolation ward and received antiviral treatment with hydroxychloroquine (400 mg every 12 hours, orally) and lopinavir plus ritonavir (400/100 mg every 12 hours, orally) combined with azithromycin (500 mg, then 250 mg, once daily, orally) for anti-inflammation. Amoxicillin plus clavulanate (1.2 g every 12 hours, intravenously) was given for continued treatment of acute exudative tonsillitis. After receiving antiviral treatment with azithromycin, the patient developed symptoms of anorexia, vomiting, and watery diarrhoea (Table 2). Favipiravir (1600 mg every 12 hours for 1 day, then 600 mg every 12 hours, orally) was added as antiviral treatment for COVID-19 pneumonia on April 14 (day 4 of illness), after awaiting for drug delivery from the hospital of Ministry of public health in Thailand.

On April 17 (day 7 of illness) (Table 2), fever raised to 39.1 ºC combined with increased symptoms of cough, myalgia, fatigue, watery diarrhoea, pleuritic chest pain, and shortness of breath, but no sore throat and no enlargement of both tonsils. Amoxicillin plus clavulanate was then stopped and cefoperazone plus

sulbactam (1.5 g every 12 hours, intravenously) was administered due to suspicion of co-infection with a hospital acquired infection. Laboratory findings showed decreased ALC (1309 cells/mm^3).

On April 18 (day 8 of illness), chest radiograph showed progression of alveolar infiltration at the right upper and right middle lung zone and increased interstitial infiltration in the left upper, middle, and lower lung zone (Figure 2C). The patient was then transferred to the ICU with negative pressure isolation due to decreased SpO_2 (87%) at room air and increased shortness of breath with a respiratory rate of 40 breaths/min. The patient received supplement oxygen via a face mask in the prone position in order to keep SpO_2>94%. Tocilizumab (8 mg/kg/dose intravenous drip for 90 min with repeated dose in the next 12 hours) was then administered to attenuate lung inflammation, as hypoxemia developed. Laboratory findings showed decreased ALC (1158 cells/mm^3) and increased levels of hs-CRP (145.4 mg/L), IL-6 (49.8 pg/mL), and LDH (380 U/L) (Table 2).

On April 19 (day 9 of illness), the symptoms showed improvement, the body temperature was reduced (37.1 ^{o}C), and SpO_2 was increased (91% at room air). Laboratory findings showed decreased ALC (1013 cells/mm^3), decreased levels of hs-CRP (120.8 mg/L) and LDH (369 U/L), and increased levels of IL-6 (865.0 pg/mL) (Table 2). On April 20 (day 10 of illness), chest radiograph showed decreased infiltration in both lungs, but new alveolar infiltration was observed in the right lower lung zone. On April 21 (day 11 of illness), laboratory findings showed increased ALC (1370 cells/mm^3) and markedly decreased hs-CRP levels (5.4 mg/L) (Table 2).

On April 22 (day 12 of illness), maculopapular rash with itching was observed at both arms and thighs. The patient received anti-histamine medications, including chlorpheniramine (10 mg every 8 hours, intravenously), diphenhydramine (50 mg once a day, orally), and cetirizine (20 mg every 12 hours, orally). Generalized maculopapular rash was then found to have spread throughout the face, neck, and trunk on April 24 (day 14 of illness) (Figure 3). The rash decreased on April 25 (day 15 of illness), at 3 days after stopping hydroxychloroquine and lopinavir plus ritonavir (Table 2).

On April 23 (day 13 of illness), ALT levels (115 U/L) were elevated and raised to 303 U/L on April 28 (day 18 of illness) (Table 2), but decreased to 240 U/L on May 3 (day 23 of illness) and to 170 U/L on May 18 (day 38 of illness).

On April 24 (day 14 of illness), chest radiograph showed mark decreased infiltration in both lungs, and SpO_2 increased (96% at room air) on April 25 (day 15 of illness) (Table 2). Haemocultures and sputum culture were negative. The patient was transferred back to the negative pressure isolation ward. Chest radiograph showed minimal interstitial infiltration at the right middle lung zone on April 28 (day 18 of illness), which was normal on May 18 (day 38 of illness) (Figure 2D). RT-PCR assay for the detection of SARS-CoV-2 RNA was negative on two repeated samples of nasopharyngeal and oropharyngeal swabs on Apr 28 (day 18 of illness) and May 15 (day 35 of illness). The patient received antiviral treatment with hydroxychloroquine and lopinavir plus ritonavir for 10 days, and favipiravir was extended to 14 days.

Case 3

A 78-year-old Thai female presented to the emergency department with right hemiparesis and drowsiness after a fall due to acute left thalamic infarction with intraventricular haemorrhage on March 21, 2020. She had underlying chronic medical illness, including hypertension, hyperlipidaemia, and paroxysmal atrial fibrillation. Physical examination showed Glasgow Coma Scale (GCS) score of 8 (E3M1V4), blood pressure of 187/84 mmHg, and motor power grade II on the right extremities. Chest radiograph showed cardiomegaly with suspicion of some degree of congestion and patchy infiltration in the right lower lung. The patient received normal saline infusion, and blood pressure was controlled in the ICU. The GCS score increased to 12 (E4M2V6), and motor power increased to grade III on the right extremities within 24 hours after treatment (Table 3).

On March 24, the patient had fever and atrial fibrillation with rapid ventricular rate of 124 beats/min. Amiodarone was administered for controlling the heart rate and blood pressure within a range of 66-92

beats/min and 129/68-164/63 mmHg, respectively. The GCS score decreased to 9 (E2M2V5), but motor power was still grade III on the right extremities. The patient had no cough and no shortness of breath, but lungs showed crepitation in both lower lobes. Chest radiograph showed increased alveolar infiltration in both the lower lung zones (Figure 4A). Laboratory findings showed leucocytosis (12270 cells/mm^3) with neutrophilia (9767 cells/mm^3), and urinalysis revealed 30-50 white blood cells/high power field. Doripenem (500 mg every 8 hours, intravenously) was then given due to suspicious hospital acquired pneumonia and urinary tract infection. Two samples of haemoculture were negative, but sputum culture showed *Klebsiella pneumoniae* , and urine culture showed*Escherichia coli* $>10^5$ CFU/mL. Both organisms were sensitive to ceftriaxone, and the antibiotic was then tapered to ceftriaxone (2 g once daily, intravenously). Between March 26 and 30, the patient had no fever, and chest radiograph showed decreased infiltration in both lower lung zones (Figure 4B).

On March 31, the patient had no fever, but she had fatigue, watery diarrhoea, increased respiratory rate (22 breaths/min), decreased SpO_2 (94%), and lung crepitation at the right upper lobe (Table 3). Chest radiograph showed alveolar infiltration at the right upper lung zone and interstitial infiltration at the left lower lung zone. Complete blood analysis showed normal white blood cell count but low ALC (892 cells/mm^3).

On April 3, the patient had dry cough, fatigue, and watery diarrhoea (Table 3). Chest radiograph showed increased alveolar infiltration at the right upper, middle, and lower lung zones but no change in the interstitial infiltration at the left upper and lower lung zones. Sputum smears for acid-fast bacilli were negative for 3 consecutive days.

On April 5, the patient still had dry cough, fatigue, and watery diarrhoea, but shortness of breath with decreased SpO2 (88% at room air) developed (Table 3). She had a contact history with four family members with confirmed COVID-19, but the duration of exposure was unknown. Chest radiograph showed progression of alveolar infiltration at the right upper, middle, and lower lung zones and at the left upper and lower lung zones (Figure 4C). Both nasopharyngeal and throat swab samples were then tested for SARS-CoV-2 RNA using RT-PCR. The results showed detectable SARS-CoV-2 RNA levels at the region of ORF1ab, N gene, NS-1, and NS-2 in both samples. Laboratory findings showed normal white blood cell count with lymphopenia (899 cells/mm^3) and mildly elevated ALT levels (51 U/L). The patient was transferred to the negative pressure isolation ward and received antiviral treatment with hydroxychloroquine (400 mg every 12 hours for 1 day, then 200 mg every 12 hours, orally), darunavir (800 mg once daily, orally) plus ritonavir (100 mg once daily, orally) and favipiravir (1600 mg every 12 hours for 1 day then 600 mg every 12 hours, orally). Azithromycin (500 mg then 250 mg once daily, orally) was given for anti-inflammation.

Between April 6 and 7, the patient had low-grade fever (37.5-38.2 ºC), cough, fatigue, watery diarrhoea, and shortness of breath (Table 4). She was then transferred to the ICU with negative pressure isolation and received supplement oxygen (3 L/min) via a nasal cannula while in the prone position, in order to keep SpO_2>94%. On April 8, the patient had shortness of breath with decreased SpO_2 (90% at room air) and received endotracheal tube intubation with ventilator support due to hypoxic respiratory failure. Chest radiograph showed increased alveolar infiltration and pleural effusion at both lungs. On April 9, she had no fever but still had dry cough and worsening hypoxemia, with a low SpO_2/fraction of inspired oxygen (FiO_2) ratio (98), determining the occurrence of severe ARDS. Laboratory findings showed a low ALC (619 cells/mm^3) and increased serum creatinine levels (>0.3 mg/dL) from baseline, determining the diagnosis of acute kidney injury (Table 4).

Between April 10 and 15, the clinical status of the patient was stable, but hs-CRP levels (273.8 mg/L) were high, and serum creatinine gradually increased (Table 4). Chest radiograph on April 15 showed increased alveolar infiltration in both lungs.

On April 16, the patient developed shock, as blood pressure was 63/32 mmHg, and the mean arterial pressure (MAP) was 42 mmHg. Norepinephrine was administered intravenously to keep MAP >65 mmHg. The patient developed bradycardia with a heart rate of 32 beats/min due to sick sinus syndrome (Figure 5) and was then on a temporary pacemaker at a pace rate of 70 beats/min; dexamethasone (4 g every 8 hours, intravenously)

was administered due to suspicious myocarditis. Chest radiograph showed decreased infiltration at the left upper lung zone but no change in both the lower and right upper lung zone infiltration. Right basal pleural effusion was slightly decreased. Hs-CRP levels were still high (228.0 mg/L), and IL-6 levels were high (358.0 pg/mL). Tocilizumab (8 mg/kg/dose intravenous drip for 90 min) was then administered in order to attenuate lung inflammation. Other laboratory findings showed high arterial blood lactate (4.5 mmol/L) and increased serum creatinine levels (2.29 mg/dL). Meropenem (1 g every 24 hours, intravenously) was administered for suspicious hospital acquired infection.

On April 17, the patient had low body temperature of 35.0 ºC but had productive cough with yellow phlegm, watery diarrhoea, and shortness of breath (Table 4). Chest radiograph showed interstitial infiltration at both lungs. Laboratory findings showed leucocytosis with neutrophilia and high serum procalcitonin (0.87 ng/mL), but decreased hs-CRP (168.0 mg/L) and arterial blood lactate (3.4 mmol/L) levels. Serum creatinine levels remained increased (2.67 mg/dL), and continuous veno-venous hemofiltration (CVVH) was then started, indicated by fluid overload.

On April 20, the patient still had shock (Table 4). Laboratory findings showed marked leucocytosis and decreased hs-CRP levels (32.0 mg/L). However, SARS-CoV-2 RNA detection using RT-PCR assay was negative on two repeated samples of nasopharyngeal and oropharyngeal swabs. Chest radiograph showed decreased infiltration in both lungs but increased left pleural effusion. Vancomycin (1 g every 48 hours, intravenously) and micafungin (100 mg every 24 hours, intravenously) were added for septic shock and presence of immunosuppression, but her clinical status did not improve. The arterial blood lactate levels raised to 9.1 mmol/L. Chest radiograph on April 21 showed diffuse alveolar infiltration in both lungs with increased right pleural effusion (Figure 4D). The patient died on April 21 due to septic shock. Urine culture showed $>10^5$ CFU/mL of *Candida albicans*and *Stenotrophomonas maltophilia* .

DISCUSSION

We reported three patients with confirmed SARS-CoV-2 infection with severe pneumonia according to the definition of WHO,[8]characterized by fever, cough, dyspnoea, bilateral lung infiltration, and SpO_2 [?]93% at room air. All patients had chronic medical illness, shown to be more common among patients with severe pneumonia (38.7%) than those without (21.0%).[4] There was one older patient (case 3) who died after developing severe ARDS, characterized by arterial oxygen tension/FiO_2 [?]100 mmHg with positive end-expiratory pressure [?]5 cmH_2O, septic shock, sick sinus syndrome, and acute kidney injury. A previous study showed that older patients with confirmed SARS-CoV-2 infection aged [?]65 years are at risk of developing ARDS (hazard ratio 3.26) and of progressing from ARDS to death (hazard ratio 6.17).[9]

Regarding exposure history, two of the patients (cases 1 and 2) were healthcare workers and had a history of exposure to a patient with COVID-19, with a time to illness development after exposure of 15 days in case 1 and 17 days in case 2. The duration of exposure to COVID-19 in case 3, who was an older patient, was unknown. Analysis of samples obtained from the upper respiratory tract, including nasopharyngeal and oropharyngeal swabs, in cases 1 and 2 showed undetectable SARS-CoV-2 RNA levels on day 14 after exposure. A previous study showed a median incubation period of 4 days among patients with COVID-19 pneumonia, which was shorter than that among our patients.[4]

The duration from the onset of symptoms to the development of pneumonia was only a few days: 3 days in case 1 and 2 days in case 2. Severe pneumonia, defined according to WHO,[8] developed on day 6 of illness in cases 1 and 3 and on day 8 in case 2. However, a previous report showed a median time from symptom onset to pneumonia development of 5 days and to severe pneumonia development of 13 days, both longer than those in our report.[10] Chest CT scan in cases 1 and 2 showed ground-glass opacity with local patchy shadowing. However, chest radiograph was normal in case 1 and showed minimal local patchy shadowing in case 2. In addition, chest radiograph in case 3 showed local patchy shadowing with interstitial abnormality. Similarly, a previous study showed abnormalities on chest radiograph in 59.1% of patients with COVID-19, which were fewer than abnormalities on chest CT scan observed in 86.2% of the patients[4]; these abnormalities included ground-glass opacity (56.4%), bilateral patchy shadowing (51.8%), local patchy shadowing (41.9%)

and interstitial abnormalities (14.7%).[4]

Laboratory findings in our patients showed normal white blood count with decreased ALC <1500 cells/mm^3. A previous study reported that lymphocytopenia, defined as ALC <1500 cells/mm^3, was present in 83.2% of patients with confirmed SARS-CoV-2 infection, and particularly in those with severe pneumonia (96.1%), those admitted to an ICU, used mechanical ventilation, or died (92.6%).[4] The levels of hs-CRP, LDH, and IL-6 were increased in our patients, consistently to what was previously reported among patients with severe pneumonia.[4,11]

A previous study showed a mortality rate of 8.1% among patients with COVID-19 with severe pneumonia and of only 0.1% among those with non-severe COVID-19.[4] No specific treatment for patients with COVID-19 has been reported, but multiple target therapy for SARS-CoV-2 infection has been recommended according to local guidelines in Thailand. Chloroquine or hydroxychloroquine combined with darunavir plus ritonavir or lopinavir plus ritonavir for 5 days should be considered for patients with mild symptoms. Patients with pneumonia should receive favipiravir for 10 days and chloroquine or hydroxychloroquine combined with darunavir plus ritonavir or lopinavir plus ritonavir for 10 days. However, azithromycin may be used in patients with pneumonia. After our patients (case 1 and case 2) were diagnosed with pneumonia, hydroxychloroquine combined with darunavir plus ritonavir and favipiravir were given in case 1 and hydroxychloroquine combined with lopinavir plus ritonavir and favipiravir were given in case 2. However, there was progression of lung infiltration and hypoxemia (SpO_2 92% at room air) in case 1 after receiving darunavir plus ritonavir for 2 days. Then, lopinavir plus ritonavir was given to replace darunavir plus ritonavir. A previous randomized controlled trial on lopinavir plus ritonavir showed no difference in time to clinical improvement and mortality between adults hospitalized with severe COVID-19 and those who received standard care.[10] In that trial, adverse events were observed in 48.4% of hospitalized patients receiving lopinavir plus ritonavir, showing gastrointestinal symptoms including nausea, vomiting, and diarrhoea as common adverse events.[10] A previous nonrandomized controlled trial showed favipiravir as an independent factor associated with faster viral clearance than that with lopinavir plus ritonavir (hazard ratio 3.43).[12] After 14 days of favipiravir in two of our patients, SARS-CoV-2 RNA was undetectable within one day and two days in cases 2 and 3, respectively, following a complete course of this antiviral therapy; however, SARS-CoV-2 RNA was still detectable for at least 24 days in case 1 following a 10-day treatment course.

With the development of severe pneumonia, which was refractory to the multiple target therapy including hydroxychloroquine combined with lopinavir plus ritonavir and favipiravir in cases 1 and 2, slow infusion of 8 mg/kg/dose tocilizumab for 90 min, with a repeated dose in the next 12 hours, was performed in order to attenuate lung inflammation. Both patients were admitted to the ICU and required supplemental oxygen therapy in the prone position in order to reach the target of SpO_2 >94%. The symptoms of both patients improved, as indicated by the rapid resolution of fever and decreased oxygen supplementation within 24 hours. The levels of hs-CRP rapidly decreased, lung opacities also decreased, and IL-6 level increased after receiving tocilizumab. This might be due to the decrease function of IL-6 as a critical mediator for the development of cytokine storms, leading to respiratory failure, shock, and organ dysfunction in patients with severe COVID-19 pneumonia.[4-6]

However, several studies have been conducted on pharmacological treatments with potential clinical benefit and adjunctive pharmacological treatments.[13] A systematic review showed that tocilizumab might be used as a potential adjunctive pharmacological treatment for patients with COVID-19, particularly for those with high IL-6 levels.[7] A previous study showed that tocilizumab dose ranged from 80 to 600 mg, with an average of 1.5 doses among 15 patients with COVID-19, 47% of whom were critically ill; the case fatality rate was 20%.[14] Further ongoing randomized controlled trials might help to clarify the benefit of tocilizumab for COVID-19.[7]

Our third patient (case 3) received hydroxychloroquine combined with darunavir plus ritonavir and favipiravir when severe pneumonia developed. After receiving this therapy for 4 days, the patient developed severe ARDS and required endotracheal intubation with mechanical ventilation due to hypoxic respiratory failure. Sick sinus syndrome with brady-arrhythmia and unstable haemodynamics requiring temporary pacemaker

developed after 6 days of therapy. Acute kidney injury was observed on day 5, and CVVH was started due to fluid overload on day 12. Septic shock also developed on day 12, and thus, one dose of tocilizumab (8 mg/kg/dose for 90 min) was administered with dexamethasone (12 mg daily). After receiving adjunctive pharmacological treatments with tocilizumab and the corticosteroid, hs-CRP levels were still high, and IL-6 levels increased. The patient died due to co-bacterial infection within 2 weeks after ICU admission. A previous study showed common complications among patients with COVID-19 with severe pneumonia, including ARDS (15.6%), septic shock (6.4%), and acute kidney injury (2.9%),[4] which was similar what we observed in case 3.

CONCLUSION

Early diagnosis and early treatment of COVID-19 pneumonia, as well as timely treatment of severe pneumonia, are important for the survival of patients with COVID-19, in order to prevent the development of cytokine storms, as a critical mediator for respiratory failure, shock, and organ dysfunction in these patients.

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Figure legends

Figure 1. Chest imaging of a 58-year-old Thai man (case 1). (A) Chest computed tomography scan on March 27, 2020 (day 3 of illness), showing ground glass infiltration at the posterior segment of the left lower lobe by air bronchogram. (B) Chest radiograph on March 29, 2020 (day 5 of illness), showing progression of interstitial infiltration in the right middle and left lower lung zone. (C) Chest radiograph on April 4, 2020 (day 11 of illness), showing new alveolar infiltration at the right upper lung zone and increased alveolar infiltration in the right middle, left upper, and left lower lung zone. (D) Chest radiograph on April 23, 2020 (day 30 of illness), was normal.

Figure 2. Chest imaging of a 34-year-old Thai female (case 2). (A) Chest radiograph on April 12, 2020 (day 2 of illness), showing minimal interstitial infiltration in the left lower lung zone. (B) Chest computed tomography scan without contrast on April 12, 2020 (day 2 of illness), showing patchy ground glass, with overlying consolidation opacity, and interlobar septal thickening at the inferior lingular segment of the left upper lobe. (C) Chest radiograph on April 18, 2020 (day 8 of illness), showing progression of alveolar infiltration at the right upper and middle lung zones and increased interstitial infiltration in the left upper, middle, and left lower lung zone. (D) Chest radiograph on May 18, 2020 (day 38 of illness), was normal.

Figure 3. Generalized maculopapular rash throughout the face, neck, and trunk in a 34-year-old Thai female (case 2), observed on April 24, 2020 (day 14 of illness).

Figure 4. Chest imaging of a 78-year-old Thai female (case 3). (A) Chest radiograph on March 24, 2020, showing increased alveolar infiltration in both lower lung zones. (B) Chest radiograph on March 26, 2020, showing decreased infiltration in both lower lung zones. (C) Chest radiograph on April 5, 2020, showing progression of alveolar infiltration at the right upper, right middle, and right lower lung zone, and at the left upper and left lower lung zone. (D) Chest radiograph on April 21, 2020, showing diffuse alveolar infiltration in both lungs with increased right pleural effusion.

Figure 5. Electrocardiography on April 16, 2020, of a 78-year-old Thai female (case 3), showing bradycardia, with a heart rate of 32 beats/min due to sick sinus syndrome.

Table 1. Symptoms and signs, laboratory findings, and management of a 58-year-old Thai man (case 1) from the day of exposure, March 11, to April 11, 2020.

Day of illness	Exposure	3 (ER)	4	5	6	7	8	9	10	11	12	13	14	15	16
Date	Mar 11	Mar 27 (Ward)	Mar 28 (Ward)	Mar 29 (Ward)	Mar 30 (Ward)	Mar 31 (Ward)	Apr 1 (Ward)	Apr 2 (Ward)	Apr 3 (Ward)	Apr 4 (ICU)	Apr 5 (ICU)	Apr 6 (ICU)	Apr 7 (Ward)	Apr 8 (Ward)	Ap 9 (W
Symptoms and signs	*Symptoms and signs*														
Fever (^{o}C)	-	37.9	38.3	37.1	37.5	37.9	37.9	38.7	38.5	38.4	37.1	36.8	37.0	37.0	37
Cough	-	++	++	++	++	++	++	+++	+++	+++	++	+	+	+	+
Sneezing	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	-	++	+	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	+	+	++	++	+++	+++	++	+	+	-	-
Anorexia	-	-	-	-	-	+	++	++	+++	+++	+++	+	+	-	-
Diarrhoea	-	-	-	-	+	++	++	+	+	+	++	+	+	-	-
SOB	-	-	-	-	+	+	++	+++	+++	+++	++	+	-	-	-
RR (breaths/min)	-	20	22	20	22	20	20	22	24	28	26	26	26	22	20
SpO_2/FiO_2 (ratio)	-	97/0.21 (462)	95/0.21 (452)	95/0.21 (452)	92/0.21 (438)	90/0.21 (428)	92/0.21 (438)	88/0.21 (419)	88/0.21 (419)	88/0.21 (419)	91/0.21 (433)	93/0.21 (443)	94/0.21 (448)	96/0.21 (457)	96 (4
HR (beats/min)	-	90	86	88	88	80	88	104	94	92	90	90	94	90	94
Laboratory findings	*Laboratory findings*														
SARS-CoV-2 RNA	undetected (Mar 24)	detected	-	-	-	-	-	-	-	-	-	-	-	-	de
Hgb (g/dL)	-	14.3	-	15.2	-	-	-	-	-	14.3	13.8	14.6	15.6	-	-
Hct (%)	-	41.3	-	43.9	-	-	-	-	-	40.7	40.0	42.2	45.5	-	-
WBC (cells/mm^3)	-	6160	-	4510	-	-	-	-	-	10460	7310	4740	4740	-	-
ANC (cells/mm^3)	-	5347	-	3324	-	-	-	-	-	9749	6667	4090	3266	-	-
ALC (cells/mm^3)	-	419	-	708	-	-	-	-	-	408	351	289	758	-	-
Plts (/mm^3)	-	258000	-	251000	-	-	-	-	-	393000	411000	495000	540000	-	-
hs-CRP (mg/L)	-	-	-	-	-	-	-	-	-	164.7	155.8	63.1	31.6	-	-
IL-6 (pg/mL)	-	-	-	-	-	-	-	-	-	46.6	784.0	-	-	-	-

Day of illness	Exposure	3 (ER)	4	5	6	7	8	9	10	11	12	13	14	15	16
ALT (U/L)	-	28	-	-	-	-	-	-	-	36	41	-	56	-	-
LDH (U/L)	-	-	-	-	-	-	-	-	-	409	-	-	-	-	-
Cr (mg/dlL)	-	1.1	-	-	-	-	-	-	-	0.9	-				
Management															
Oxygen (L/min)	-	-	-	-	NC (5)	NC (5)	NC (5)	NC (5)	NC (5)	NC (5)	NC (5)	NC (5)	NC (5)	NC (3)	NC (3)
Hydroxychloroquine	-		400 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	-	-	-
Darunavir + Ritonavir	-		800/100 mg	800/100 mg	-	-	-	-	-	-	-	-	-	-	-
Lopinavir + Ritonavir	-		-	-	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100-
Favipiravir	-		-	-	1600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	-
Tocilizumab	-		-	-	-	-	-	-	-	560 mg	560 mg	-	-	-	-
Azithromycin	-		500 mg	500 mg	500 mg	500 mg	500 mg	-	-	-	-	-	-	-	-

Abbreviations: ALT = alanine aminotransferase; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Cr = creatinine; ER = emergency room; FiO_2 = fraction of inspired oxygen; Hgb = haemoglobin, Hct = haematocrit; HR = heart rate; hs-CRP = high sensitivity C-reactive protein; ICU = intensive care unit; IL-6 = interleukin-6; LDH = lactate dehydrogenase; NC = nasal cannula; Plts = platelets; RR = respiratory rate; SOB = shortness of breath; SpO_2 = arterial oxygen saturation; WBC = white blood cell count

Table 2. Symptoms and signs, laboratory findings, and management of a 34-year-old Thai female (case 2) from the day of exposure, March 26, to April 28, 2020.

Day of illness	Exposure	1 (ARI clinic)	2	3	4	5	6	7	8	9	10	11	12	13	14

Day of illness	Exposure	1 (ARI clinic)	2	3	4	5	6	7	8	9	10	11	12	13	14

Date	Mar 26	Apr 11	Apr 12 (Ward)	Apr 13 (Ward)	Apr 14 (Ward)	Apr 15 (Ward)	Apr 16 (Ward)	Apr 17 (Ward)	Apr 18 (ICU)	Apr 19 (ICU)	Apr 20 (ICU)	Apr 21 (ICU)	Apr 22 (ICU)	Apr 23 (ICU)	Ap 24 (W
Symptoms and signs	*Symptoms and signs*														
Fever (ºC)	-	38.6	37.0	38.1	38.8	38.5	38.3	39.1	38.7	37.1	36.8	35.9	36.8	36.1	36
Cough	-	-	+	+	+	+	+	++	+++	+++	+++	+++	++	++	+
Sore throat	-	++	++	+	+	+	-	-	-	-	-	-	-	-	-
Myalgia	-	-	++	++	++	++	++	++	++	++	++	+	-	-	-
Fatigue	-	-	+	+	+	+	++	+++	+++	++	+	-	-	-	-
Anorexia	-	-	-	+++	+++	+++	+++	+++	+++	++	++	++	+	-	-
Vomiting	-	-	-	+++	+++	+++	+++	+++	+++	++	++	+	+	-	-
Diarrhoea	-	-	-	-	-	+	+	++	++	+++	+	-	-	-	-
Pleurisy	-	-	-	-	-	-	-	+	+++	++	+	-	-	-	-
SOB	-	-	-	-	-	-	-	+	+++	++	++	++	++	++	+
Rash	-	-	-	-	-	-	-	-	-	-	-	-	++	+++	+
RR (breaths/min)	-	-	18	20	22	22	24	26	40	34	32	28	24	24	22
SpO_2/FiO_2 (ratio)	-		96/0.21 (457)	96/0.21 (457)	95/0.21 (452)	95/0.21 (452)	95/0.21 (452)	95/0.21 (452)	87/0.21 (414)	91/0.21 (433)	90/0.21 (428)	90/0.21 (428)	91/0.21 (433)	90/0.21 (428)	92 (4
HR (beats/min)	-	-	106	102	116	110	104	120	122	100	92	82	82	82	82
Laboratory findings	*Laboratory findings*														
SARS-CoV-2 RNA	undetected (Apr 8)	detected	-	-	-	-	detected	-	-	-	-	-	-	-	-
Hgb (g/dL)	-	-	13.9	-	-	-	-	14.6	14.4	13.8	-	14.7	-	15.2	-
Hct (%)	-	-	41.7	-	-	-	-	43.3	42.5	40.8	-	44.5	-	46.2	-
WBC (cells/mm^3)	-	-	7880	-	-	-	-	6580	8980	5630	-	2490	-	3130	-
ANC (cells/mm^3)	-	-	5752	-	-	-	-	4988	7408	4448	-	946	-	1240	-
ALC (cells/mm^3)	-	-	1592	-	-	-	-	1309	1158	1013	-	1370	-	1440	-
Plts (/mm^3)	-	-	203000	-	-	-	-	237000	299000	307000	-	373000	-	448000	-

Day of illness	Exposure	1 (ARI clinic)	2	3	4	5	6	7	8	9	10	11	12	13	14
hs-CRP (mg/L)	-	-	89.6	-	-	-	-	74.3	145.4	120.8	-	5.4	-	1.3	-
IL-6 (pg/mL)	-	-	-	-	-	-	-	-	49.8	865.0	-	-	-	-	-
ALT (U/L)	-	-	19	-	-	-	-	27	-	-	-	-	-	115	-
LDH (U/L)	-	-	-	-	-	-	-	-	380	369	-	-	-	323	-
Cr (mg/dL)	-	-	0.6	-	-	-	-	0.7	-	0.6	-	-	-	0.9	-
Management															
Oxygen (L/min)	-	-	-	-	-	-	-	-	FM (10)	NC (5)	NC (5)	NC (3)	NC (3)	NC (3)	NC (3)
Hydroxychloroquine	-		400 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	-	-	-
Lopinavir + Ritonavir	-		400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	400/100 mg q 12 h	-	-	-
Favipiravir	-		-	-	1600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h
Tocilizumab	-		-	-	-	-	-	-	560 mg	560 mg	-	-	-	-	-
Azithromycin	-		500 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

Abbreviations: ARI = acute respiratory infection; ALT = alanine aminotransferase; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Cr = creatinine; FiO_2 = fraction of inspired oxygen; FM = face mask; Hgb = haemoglobin, Hct = haematocrit; HR = heart rate; hs-CRP = high sensitivity C-reactive protein; ICU = intensive care unit; IL-6 = interleukin-6; LDH = lactate dehydrogenase; NC = nasal cannula; Plts = platelets; RR = respiratory rate; SpO_2 = arterial oxygen saturation; SOB = shortness of breath; WBC = white blood cell count

Table 3. Symptoms and signs, laboratory findings, and management of a 78-year-old Thai female (case 3) from the day of hospitalization, March 21, to April 5, 2020.

Day of illness	1 (ER)	2	3	4	5	6	7	8	9	10	11	12	13
Date	Mar 21 (ICU)	Mar 22 (ICU)	Mar 23 (ICU)	Mar 24 (ICU)	Mar 25 (ICU)	Mar 26 (ICU)	Mar 27 (Ward)	Mar 28 (Ward)	Mar 29 (Ward)	Mar 30 (Ward)	Mar 31 (Ward)	Apr 1 (Ward)	Apr (War
Symptoms and signs													
Fever (^{o}C)	37.2	36.5	36.4	38.4	37.5	36.9	36.6	36.8	36.7	36.6	37.0	36.6	36.3
Cough	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-	-	-	-	+	+	+
Diarrhoea	-	-	-	-	-	-	-	-	-	-	++	+	+
SOB	-	-	-	-	-	-	-	-	-	-	-	-	-
RR (breaths/min)	14	18	20	16	18	20	20	20	22	22	22	20	20
SpO_2/FiO$_2$ (ratio)	98/0.21 (467)	98/0.21 (467)	97/0.21 (462)	98/0.21 (467)	98/0.21 (467)	98/0.21 (467)	97/0.21 (462)	98/0.21 (467)	96/0.21 (457)	97/0.21 (462)	94/0.21 (448)	95/0.21 (452)	95/0 (452
HR (beats/min)	82	112	108	124	110	108	96	88	86	86	90	94	72
Glasgow coma scale	E3M1V4	E4V2M6	E4V2M6	E2V2M5	E3V2M5	E3V4M5	E3V4M5	E3V4M5	E3V5M6	E3V5M6	E3V4M5	E3V4M5	E3V
Laboratory findings													
SARS-CoV-2 RNA	-	-	-	-	-	-	-	-	-	-	-	-	-
Hgb (g/dL)	14.4	-	-	13.5	-	-	-	11.4	-	-	-	13.5	-
Hct (%)	42.2	-	-	39.0	-	-	-	33.5	-	-	-	39.3	-
WBC (cells/mm^3)	7320	-	-	12270	-	-	-	7520	-	-	-	8580	-
ANC (cells/mm^3)	3945	-	-	9767	-	-	-	5866	-	-	-	6735	-
ALC (cells/mm^3)	2481	-	-	994	-	-	-	850	-	-	-	892	-
Plts (/mm^3)	185000	-	-	172000	-	-	-	275000	-	-	-	301000	-
ALT (U/L)	22	-	-	-	-	-	-	-	-	-	-	-	-
Cr (mg/dL)	0.6	-	0.6	-	-	-	0.8	0.8	0.8	-	0.6	-	-
Management													
Oxygen (L/min)	-	-	-	-	-	-	-	-	-	-	NC (3)	NC (3)	NC (3)

Day of illness	1 (ER)	2	3	4	5	6	7	8	9	10	11	12	13
Manidipine	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Hydralazine	-	-	-	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Metoprolol	-	-	-	50 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	25 mg
Amiodarone	-	-	-	400 mg	400 mg	400 mg	200 mg	200 mg	200 mg	100 mg	-	-	-
Darunavir + Ritonavir	-	-	-	-	-	-	-	-	-	-	-	-	-
Hydroxychloroquine	-	-	-	-	-	-	-	-	-	-	-	-	-
Favipiravir	-	-	-	-	-	-	-	-	-	-	-	-	-
Azithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: ALT = alanine aminotransferase; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Cr = creatinine; FiO_2 = fraction of inspired oxygen; Hgb = haemoglobin, Hct = haematocrit; HR = heart rate; hs-CRP = high sensitivity C-reactive protein; ICU = intensive care unit; IL-6 = interleukin-6; LDH = lactate dehydrogenase; NC = nasal cannula; Plts = platelets; RR = respiratory rate; SpO_2 = arterial oxygen saturation; WBC = white blood cell count

Table 4. Symptoms and signs, laboratory findings, and management of a 78-year-old Thai female (case 3) between April 6 and April 21, 2020.

Day of illness	17	18	19	20	21	22	23	24	25	26	27	28	29
Date	Apr 6 (ICU)	Apr 7 (ICU)	Apr 8 (ICU)	Apr 9 (ICU)	Apr 10 (ICU)	Apr 11 (ICU)	Apr 12 (ICU)	Apr 13 (ICU)	Apr 14 (ICU)	Apr 15 (ICU)	Apr 16 (ICU)	Apr 17 (ICU)	Apr 18 (ICU
Symptoms and signs													
Fever (^oC)	37.5	38.2	37.2	36.5	35.8	36.0	36.3	35.7	35.0	35.0	35.0	35.0	35.0
Cough	+	+	+	+	+	+	+	+	+	+	+	+	+
Fatigue	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diarrhoea	++	++	++	++	++	+	+	++	++	+	-	-	+
Dyspnoea	++	++	++	++	++	++	++	+++	++	++	+++	+++	+++

Day of illness	17	18	19	20	21	22	23	24	25	26	27	28	29
RR (breaths/min)	24	26	24	28	28	28	28	30	24	24	28	30	32
SpO_2/FiO_2 (ratio)	95/0.21 (452)	93/0.21 (443)	90/0.21 (428)	88/0.9 (98)	91/0.9 (101)	94/0.9 (104)	88/0.9 (98)	85/0.9 (94)	94/0.8 (118)	94/1.0 (94)	83/1.0 (83)	91/1.0 (91)	94/0 (134
HR (beats/min)	106	92	82	74	68	74	68	76	64	48	32	76	78
Glasgow coma scale	E3V5M6	E3V5M6	E2V5M6	E1VTM5	E1VTM5	E1VTM4	E1VTM4	E1VTM4	E1VTM1	E1VTM1	E1VTM1	E1VTM1	E1V
Laboratory findings													
SARS-CoV-2 RNA	-	-	-	-	-	-	-	-	-	-	-	-	-
Hgb (g/dl)	-	-	-	11.7	-	-	-	11.1	11.8	-	12.9	10.7	8.3
Hct (%)	-	-	-	34.3	-	-	-	32.5	34.9	-	37.4	32.0	24.5
WBC ($cells/mm^3$)	-	-	-	8720	-	-	-	8220	6930	-	9530	15030	1359
ANC ($cells/mm^3$)	-	-	-	7534	-	-	-	6896	5696	-	8853	14263	1220
ALC ($cells/mm^3$)	-	-	-	619	-	-	-	468	457	-	200	346	557
Plts ($/mm^3$)	-	-	-	280000	-	-	-	229000	190000	-	204000	50000	1070
hs-CRP (mg/L)	-	-	-	-	273.8	-	-	-	-	-	228.0	168.0	-
IL-6 (pg/mL)	-	-	-	-	-	-	-	-	-	-	358.0	2678.0	-
ALT (U/L)	-	-	-	-	44	-	40	42	43	110	-	-	-
Cr (mg/dL)	-	-	-	1.04	1.26	1.22	1.21	1.46	-	1.95	2.29	2.67	1.50
Procalcitonin (ng/mL)	-	-	-	-	-	-	-	-	-	-	-	0.87	-
Lactate (mmol/L)	-	-	-	-	-	-	-	-	-	-	4.5	3.4	-
Management													
Oxygen supplement (L/min)	NC (3)	NC (3)	NC (3)	MV	MV	MV	MV	MV	MV	MV	MV	MV	MV

Day of illness	17	18	19	20	21	22	23	24	25	26	27	28	29
Manidipine	20 mg	-	-	-	-	-	-	-	-	-	-	-	-
Hydralazine	50 mg	37.5 mg	-	-	-	-	-	-	-	-	-	-	-
Metoprolol	25 mg	25 mg	-	-	-	-	-	-	-	-	-	-	-
Darunavir + Ritonavir	800/100 mg	800/100 mg	800/100 mg	800/100 mg	800/100 mg	800/100 mg	800/100 mg	800/100 mg	800/100 mg	-	-	-	-
Hydroxychloroquine	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	200 mg q 12 h	-	-	-	-
Favipiravir	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h	600 mg q 12 h
Azithromycin	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Tocilizumab	-	-	-	-	-	-	-	-	-	-	560 mg	-	-

Abbreviations: ALT = alanine aminotransferase; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Cr = creatinine; FiO_2 = fraction of inspired oxygen; Hgb = haemoglobin, Hct = haematocrit; HR = heart rate; hs-CRP = high sensitivity C-reactive protein; ICU = intensive care unit; IL-6 = interleukin-6; LDH = lactate dehydrogenase; MV = mechanical ventilation; NC = nasal cannula; Plts = platelets; RR = respiratory rate; SpO_2 = arterial oxygen saturation; WBC = white blood cell count