Clinical course of 11 cases of SARS-CoV-2 infection occurred in a large cruise ship

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Abstract

The clinical course of 11 cases of SARS-CoV-2 infection in a large cruise ship is summarised. The day when any symptoms appeared on board was defined as the first illness day. Severity was determined using the Chinese CDC classification. The median age of the 11 cases was 62 years, 4 men and 7 women. Initial symptoms were cough in 4 (36.4%) and fever in 3 (27.3%). There were 7 mild cases, 4 moderate cases, and 0 severe cases. Various levels of gastrointestinal symptoms frequently occurred in patients treated with Lopinavir/ritonavir, and one patient with heart disease led to discontinued due to arrhythmia. A comparison of the patient background, laboratory findings, and clinical course from the date of onset between mild and moderate cases shows that moderate cases are older, have elevated serum amyloid protein and ferritin, and have decreased IgA. The median time from onset to remission in mild cases were 6 days shorter than those in moderate cases, but the median days before PCR became negative were only two days apart. The median time from onset to discharge was 22.5 days for moderate cases and 16 days for mild cases. This data indicates that most non-severe cases require hospitalisation for at least 2 weeks after the onset in Japan. In addition, even in mild cases whose symptoms have resolved in a relatively short period of time since onset, PCR of the oropharyngeal or nasopharyngeal swab in some patients has detected with a high viral load of SARS-CoV-2, which may continue to be a potential source of infection. It was considered necessary to appropriately select patients at high risk of illness or those that could be a long-term source of infection.

Introduction

In February 2020, an outbreak of SARS-CoV-2 infection (COVID-19) occurred in a large cruise ship calling at Yokohama Port [1)]. Eleven cases of COVID-19, including passengers and crew hospitalised in our hospital. During the quarantine period, daily thermometry and health surveys were conducted, so that for patients who developed infectious disease within a certain period, the date of onset could be accurately determined regardless of the severity. In addition, patients with COVID-19, designated an infectious disease, are eligible for admission to the hospital and should continue to be hospitalised until they meet certain discharge criteria. We believe that it will help accumulate clinical knowledge in the future, so we will report mainly on the clinical course of individual cases

Method and Results

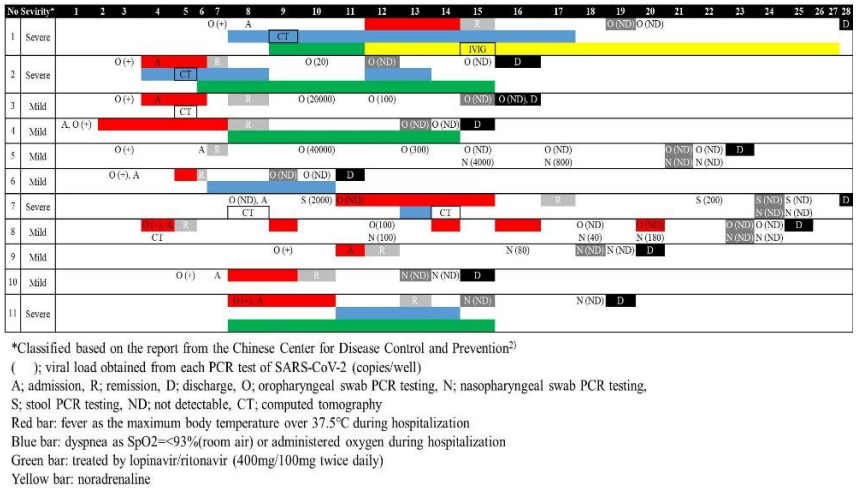
A total of 11 patients who were admitted to our hospital with COVID-19 during the quarantine period in a large cruise ship were targeted. COVID-19 was defined as any clinical manifestation in addition to a positive PCR test

on any sample taken for screening or diagnostic purposes. The day when any symptoms appeared, not limited to fever and respiratory symptoms, was defined as the first illness day. Initial symptoms and symptoms that appeared during the entire course were investigated. Severity was classified based on the classification published by the CDC of China [2]. However, the class named "Mild", “Severe”, and “Critical” classified by the CDC of China defined as “Mild “, “Moderate”, and “Severe” in this report, respectively. For patients who did not perform arterial blood gas analysis, percutaneous arterial oxygen saturation (SpO_2) was used instead of arterial oxygen saturation (SaO_2). The discharge criteria are as follows: "After remission, perform a PCR test every 48 hours and, if negative, collect the sample again 12 hours after the previous sample collection, and confirm the negative twice consecutively." The definition of “remission” was defined as "no fever of 37.5 °C or higher for 24 hours and respiratory symptoms tended to improve" [3]. Initially, the specimen used for confirming the negativity of PCR test was an oropharyngeal swab, but after February 21, 2020, a sputum and a nasopharyngeal swab (but it is difficult to collect the sputum, a naso pharyngeal swab only). Foreign nationals are to comply with national discharge standards. The PCR test to confirm the negative conversion was performed by the real-time quantitative RT-PCR method, and it was defined as "negative" if it was below the detection limit. Table 1 shows the characteristics of the 11 patients, and Figure 1 shows the clinical course from onset to discharge. Patients’ number were assigned in ascending order of hospitalisation date. The median age was 62 years old, with 4 males, 7 females, 8 passengers and 3 crews. The initial symptoms were cough in 4 (36.4%) and fever in 3 (27.3%), and the other 4 (36.4%) had symptoms other than fever and cough. Symptoms that appeared during the entire course were fever, cough, sore throat, diarrhea and headache, in that order. The severity was 7 in “Mild” (63.6%), 4 in “Moderate” (36.4%), and 0 in “Severe”.

No	Age	Sex	Nationality		Initial symptoms	Fever	Cough	Sore throat	Headache	Fatigue	Abdominal pain	Diarrhea	Underlying disease
1	70	M	Canada	Passenger	Cough	+	+	−	−	−	−	−	1st-degree AVB, BA
2	68	F	Canada	Passenger	Cough	+	+	−	−	−	−	+	DM (HbA1c 6.5%)
3	50	M	New Zealand	Passenger	Cough	+	+	+	−	+	−	+	DM (HbA1c 7.8%)
4	37	F	China	Passenger	Fever	+	−	+	+	−	−	−	1st-trimester pregnancy
5	78	F	US	Passenger	Cough	−	+	+	+	−	−	+	RA (tofacitinib and hydroxychlorquine), DM (HbA1c 6.6%), BA
6	71	M	Japan	Passenger	Headache	+	+	−	+	−	−	−	DM (HbA1c 7.3%)
7	81	F	Japan	Passenger	Abdominal pain and diarrhea	+	−	+	−	−	+	+	Post total gastrectomy due to gastric cancer 5 years before admission
8	25	M	US	Crew	Fever	+	−	−	−	−	−	−	
9	27	F	Philippines	Crew	Fever	+	+	+	+	−	−	+	
10	33	F	Philippines	Crew	Sore throat	+	+	+	−	−	−	−	
11	62	F	China	Passenger	Headache	+	−	−	+	−	−	−	
					Frequency	90.9%	63.6%	54.5%	45.5%	9.1%	9.1%	45.5%	

M; male, F; female, AVB; atrioventricular block, BA; bronchial asthma, DM; diabetes mellitus, RA; rheumatoid arthritis

Table 1. Patients’ background and symptoms



*Classified based on the report from the Chinese Center for Disease Control and Prevention[2]
( ); viral load obtained from each PCR test of SARS-CoV-2 (copies/well)
A; admission, R; remission, D; discharge, O; oropharyngeal swab PCR testing, N; nasopharyngeal swab PCR testing,
S; stool PCR testing, ND; not detectable, CT; computed tomography
Red bar: fever as the maximum body temperature over 37.5℃ during hospitalization
Blue bar: dyspnea as SpO2=<93%(room air) or administered oxygen during hospitalization
Green bar: treated by lopinavir/ritonavir (400mg/100mg twice daily)
Yellow bar: noradrenaline

Fig. 1. Clinical course

Case 1 had congestive heart failure with first-degree atrioventricular block and pleural effusion other than pneumonia. Hypogammaglobulinemia (IgG; 296mg/dL, IgA; 140mg /dL, IgM; 8mg/dL) and urinary Bence Jones protein (λ-type M protein) were detected, as well as orthostatic hypotension. Although cardiac amyloidosis was suspected, no pathological tests were performed to confirm the diagnosis. Although lopinavir /ritonavir (LPV/RTV) was administered for pneumonia with respiratory failure, in addition to nausea, ventricular replacement rhythm caused by deterioration of known atrioventricular block was observed, and on the third day of administration, LPV/RTV was discontinued. Intravenous globulin therapy was performed for hypogammaglobulinemia. Oxygen administration during the course was as small as 1-2 L /min. After discontinuation of LPV/RTV, the ECG returned to the original first-degree atrioventricular block, but it was difficult to manage hemodynamics for congestive heart failure and prominent orthostatic hypotension, and continued hospitalisation even after meeting discharge criteria. The patient was admitted to the ICU due to long-term administration of noradrenalin, but did not developed respiratory failure or septic shock requiring mechanical ventilation. Therefore, this case was classified as “moderate”.

In Case 2, LPV/RTV was administered for 10 days for pneumonia. A small amount of watery stool was seen during LPV/RTV administration. The criteria for remission were met the day after the start of LPV/RTV treatment, but the PCR test of the oropharyngeal swab on the 10^{th} day was positive and became negative after the 12nd day.

Case 3 is a case of mild pneumonia identified only by CT scan, which met the criteria for remission on the 8th day, but the PCR test of the oral pharyngeal swab was positive on the 10th and the 12nd day, and became negative on the 15th day.

Case 4 was 14 weeks pregnant at admission. On the eighth day, although fever was improved, cough was prolonged and chest radiographs showed worsened. LPV/RTV was administered. No side effects were seen other than mild appetite loss. There were no problems with the child's development during the hospital stay.

Case 5 had been taking tofacitinib and hydroxychloroquine (not covered by insurance in Japan as of March 2020) 300mg/day for rheumatoid arthritis. After admission, she discontinued tofacitinib and continued taking hydroxychloroquine 200mg/day. No fever or hypoxemia was seen during the hospital stay. The criteria for remission were met on the 6th day, but the PCR test of the oropharyngeal swab on the 10th and 13th days was positive. The PCR test for oropharyngeal swabs became negative after the 15th day of disease, but since she was from the United States, she was required to confirm both oropharyngeal swabs and nasopharyngeal swabs as discharge conditions. PCR testing of the nasopharyngeal swab turned negative after 21 days from onset.

Case 6 was disembarked and admitted to our hospital for scrutiny and treatment of headache. The PCR test of the oropharyngeal swab collected at the time of disembarkation revealed positive the day after admission. A cerebrospinal fluid test was performed, but PCR test was not performed on the cerebrospinal fluid because the pleocytosis of cerebrospinal fluid was absent. He developed temporary fever and cough after admission, but met the criteria for remission on the sixth day.

Case 7 was disembarked and admitted to our hospital for further examination and treatment for abdominal pain and diarrhea. CT on admission showed no pneumonia. The PCR test of the oropharyngeal swab sample collected at the time of disembarkation revealed negative on the next day after admission. However, a positive PCR test was performed on diarrheal stool collected after hospitalisation, and the patient was diagnosed with SARS-CoV-2 enteritis. A PCR test of the oropharyngeal swab re-examined after hospitalisation was also negative. Although diarrhea improved on the 11st day, fever began on the same day, and hypoxemia was observed on the 13rd day. Re-examined CT showed small infiltration shadows and ground-glass shadows in the bilateral peripheral lung fields, and a diagnosis of SARS-CoV-2 pneumonia was made. The PCR of solid stool collected on the 22nd day was positive and became negative after the 24th day.

Case 8 had no symptoms other than fever during the entire course. On the day after the hospitalisation, the patient met the criteria for remission, but after that intermittent fever of 37.5°C to 37.6°C was observed. Because of US citizenship, a negative PCR test was required for oropharyngeal swabs and nasopharyngeal swabs. In particular, the PCR test of the nasopharyngeal swab remained positive until the 23rd day from onset.
Cases 9 and 10 were mild cases with mainly upper respiratory symptoms. In both cases, more than one week had passed from onset to hospitalisation, and the criteria for remission were met one and three days after hospitalisation, respectively. The length of hospital stay was relatively short, at 11 and 9 days, respectively.
In Case 11, LPV/RTV administration was started because a relatively large area of ground glass (opacity) was seen on both sides of the chest x-ray at the time of admission. There was a slight loss of appetite during the treatment. On the eleventh day of treatment, hypoxemia appeared, but on the twelfth day the criteria for remission were met.
Table 2 compares the blood test results and hospitalisation of four patients with “Moderate” and seven patients with “Mild”. The moderate cases were older than the mild cases, with higher serum ferritin and serum amyloid protein (SAA) and slightly lower IgA. In particular, SAA was over 20μg/mL in all “moderate” cases. CRP and LDH were slightly higher in moderate cases. Procalcitonin was low in both cases. SP-D had less than the detection sensitivity in more than half of the “mild” cases. In this study, lymphocyte count and D-dimer were similar in both groups. The median time from onset to meeting the criteria for remission were 13 days for moderate cases and 7 days for mild cases. The median time from onset to the confirmation of negative PCR was 16 days for moderate cases and 14 days for mild cases. The median days from onset to discharge and hospitalisation were 22.5 and 16 days for moderate cases, respectively, and 16 and 12 days for mild cases, respectively.

	All (n=11)	Moderate (n=4)	Mild (n=7)
Age, median	62	69	37
Male (%)	36.4	25	42.9
Comorbidities (%)	54.5	50	57.1
Body temperature on admission, median (°C)	37.3	36.9	37.3
Heart rate on admission, median (/min)	85	83.5	85
Systolic blood pressure on admission, median (mmHg)	124	126.5	124
Diastolic blood pressure on admission, median (mmHg)	75	69	80
Respiratory rate on admission, median (/min)	17	17	17
SpO_2 on admission, median (%) ※room air	97	95.5	98
Alb, median (g/dL)	4.1	3.65	4.3
CK, median (IU/L)	70	80.5	70
AST, median (IU/L)	24	38.5	19
ALT, median (IU/L)	28	38	25
LDH, median (IU/L)	165	294	147
ALP, median (IU/L)	169	233.5	169
BUN, median (mg/dL)	13	11.5	13
Cre, median (mg/dL)	0.71	0.785	0.68
Ferritin, median (mg/dL)	102.9	340.3	95
T-Bil, median (mg/dL)	0.4	0.4	0.5
CRP, median (mg/dL)	0.61	2.375	0.49
Serum amyloid A, median (μg/mL)	26.5	168.5	17.8
IgG, median (mg/dL)	1190	1287	1190
IgA, median (mg/dL)	234	163	279
IgM, median (mg/dL)	65	51.5	76
HbA1c, median (%)	6.5	6.5	5.9
KL-6, median (U/mL)	218	245.5	166
SP-D, median (ng/mL)	38.05	38.05	<17.2
Procalcitonin, median (ng/mL)	0.03	0.035	0.02
WBC, median (/μL)	4340	4535	4340
Neu, median (%)	63.75	66.25	63.75
Lym, median (%)	27.95	27.5	27.95
PT-INR, median	1.03	1.02	1.03
aPTT, median (sec)	27.4	27.35	27.6
Fib, median (mg/dL)	317.5	442	283
D-dimer, median (μg/mL)	0.55	0.8	0.5
Time from onset to admission, median (days)	5	7	3
Time from onset to remission, median (days)	7	13	7
Time from onset to first negative result of PCR, median (days)	14	16	14
Time from onset to discharge, median (days)	18	22.5	15
Duration of hospitalization, median (days)	12	16	12

Table 2. Comparison between “moderate” and “mild” patients

Discussion

All patients treated by LPV/RTV had various gastrointestinal symptoms as side effects, and Case 1 showed arrhythmia accompanied by decreased blood pressure and heart failure. Case 1 had first-degree atrioventricular block since admission and had some heart disease including cardiac amyloidosis. In general, atrioventricular block is likely to be complicated in patients with a history of ischemic heart disease [4], and it is necessary to pay attention to the appearance of arrhythmia when administering LPV/RTV to patients with underlying heart disease [5]. At the same time, aging and the complication of heart disease as an underlying disease are also risk factors for the severity of COVID-19 [6]. Thus, elderly patients with heart disease, such as Case 1, have risk factors for both severe COVID-19 and LPV/RTV arrhythmias. Compared to many HIV-infected patients who had previously received this drug, patients with COVID-19 who are considered to receive this drug are expected to have a higher risk of arrhythmia due to aging and underlying diseases. Careful follow-up is required when administering LPV/RTV.

Case 5 developed COVID-19 while taking hydroxychloroquine and tofacitinib, which also inhibits JAK2, for rheumatoid arthritis. Although there is a report on the inhibitory effect of balicitinib on JAK2 [7] and hydroxychloroquine [8], its preventive effect is not well understood. Additionally, the dose of hydroxychloroquine for which efficacy was reported differs from Japanese insurance dose[8], so even patients taking this drug, such as Case 5, may develop COVID-19.

According to the results of our hospital, it takes over two weeks from the onset to reach a negative PCR test for patients with COVID-19 even in “non-severe” cases. It is clear that long-term hospitalisation is required for both mild and moderate cases according to “present” discharge criteria. Also, as in Cases 3 and 5, even if mild cases meet the criteria for remission at an early stage (both on the eighth day of disease), high viral load of SARS-CoV-2 may be detected. Some patients may still be strong spreaders even after the remission of symptoms. Therefore, current discharge criteria that require a negative PCR test may be effective in preventing secondary infection. However, to consider that even mild cases require hospitalisation for about two weeks from the date of onset, some regions and medical institutions may become insufficient hospital beds near future. In this study, SAA and serum ferritin were higher in moderate cases than in mild cases. Both are nonspecific laboratory findings that are elevated in various inflammatory conditions, including viral infections, but may be useful in differentiating between moderate and mild cases. Procalcitonin is negative regardless of its severity, and positive patients should be considered for diseases other than COVID-19 or their complications. IgA tended to be slightly lower in moderate cases. There have been some case reports in Japan mentioning that IgA may contribute to spontaneous remission of COVID-19 [9], and lower IgA levels in patients with underlying diseases such as hypogammaglobulinemia such as Case 1 may also contribute to aggravation.

Limitations of this study are: (1) Cases classified as "Critical" in CDC of China, which are “severe” cases, were not included; (2) Since the number of cases is very small, statistical analyses were not conducted comparing moderate cases and mild cases.

Conclusion

Although mild cases can meet the criteria of remission relatively in early phase, it may take some time for the oropharyngeal or nasopharyngeal swabs to be negative for PCR, and some patients may be strong spreaders even after remission. Even for non-severe patients with COVID-19, it takes about 2-3 weeks from onset to meet “present” criteria for discharge. An increase in the number of early diagnosis cases due to an improvement in test sensitivity may result in insufficient hospital beds. Moderate cases tended to be more elderly than mild cases, tended to have higher SAA and serum ferritin, and lower IgA, but these were cross-sectional evaluations on admission. We believe that, by the accumulation of future cases, it is necessary to establish a method for early

detection of severe cases and cases with long-term infectivity, and to reflect this in hospitalization and discharge criteria for prevention of secondary infection.

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