Risk factors for the severe COVID-19 pneumonia

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Abstract

Currently, for new coronavirus infections (infections caused by SARS-CoV2), the administration of antiviral drugs that are indicated for other diseases is recommended when hypoxemia is observed in those aged 50 years or older. However, there are no reports examining the severity of factors that require treatment. A retrospective study was conducted on patients who were hospitalised with COVID-19 and who needed treatment with antiviral drugs, and those who improved only with follow-up, and examined clinical symptoms and clinical data that required antiviral drugs. The treatment guidelines for COVID-19 based on severity are discussed. First, 28 patients with COVID-19 who were admitted to our hospital: Group A: SARS-CoV2 PCR test positive without symptoms, Group B: Symptoms, no viral pneumonia, Group C: Symptoms, viral pneumonia, no treatment, remission, Group D: Symptoms, viral pneumonia, group requiring treatment. The only symptom that correlated with severity and was characteristic of Group D requiring treatment was diarrhea. The clinical laboratory values that correlated with the severity were lymphocyte count, D-dimer, CRP, and ferritin, but values that were significantly different between the untreated group C and the group D requiring treatment were lymphocyte count, CRP and ferritin. When the cut-off value for discriminating between the two groups was determined from the ROC curve, the lymphocyte count was 1,000/μL or less, CRP 4.16 or more, and ferritin 434 or more. On imaging findings, the best distinction between group C that did not require severe treatment and group D that required it was the presence or absence of infiltrates. Choosing five risk factors: diarrhea, lymphocyte count ≤ 1,000, ferritin 430ng/mL or higher, CRP 2.5mg/dL or higher, and CT infiltration shadow, it showed a strong correlation with the number of days from onset to negative PCR (P = 0.0002). Based on the above, the CT findings of viral pneumonia and the five severities were considered to be the criteria for starting antiviral drug treatment.

Background

As of March 27, 2020, the number of new coronavirus infections (infections caused by SARS-CoV2) has exceeded 1,200 in Japan, and the stage of the spread of community-acquired infections from imported infections has reached. However, reports on treatment with antiviral drugs are limited[1, 2], and there are currently no treatments for COVID-19 in Japan. However, clinical trials of lopinavir/ritonavir, favipiravir, and ciclesonide in patients with COVID-19 are currently ongoing in Japan. The Japanese Association for Infectious Diseases has provided guidelines for the target of antiviral drugs and the timing of initiation, and the administration of antiviral drugs should be considered when hypoxemia is observed in those aged 50 years or older[3]. For patients with diabetes, cardiovascular disease, chronic obstructive pulmonary disease due to smoking, immunosuppression, etc. the administration of antiviral drugs would be also considered. However, there are no reports examining the validity of these criteria in domestic cases.

In this study, we retrospectively examined the group of patients admitted to our hospital with COVID-19 who required treatment with antiviral drugs and those who improved only with follow-up. The clinical data were reviewed and some considerations were given regarding COVID-19 treatment guidelines based on severity.

Method

[Test design]

The study was a retrospective observational study without intervention.

From February 7, 2020 to March 18, 2020, 28 patients who were hospitalised with a positive SARS-CoV-2 PCR test were classified into the following four groups and their clinical data were compared.

Group A: Asymptomatic pathogen carriers

Group B: Symptoms, no viral pneumonia

Group C: Symptoms, viral pneumonia, no treatment and remission

Group D: Symptoms, viral pneumonia, group requiring antiviral treatment

Group D treated with antivirals required oxygen during the course of all cases, and extensive pneumonia revealed a need for antivirals. The presence or absence of viral pneumonia was determined by multiple respiratory physicians and radiologists on CT images.

[Ethical aspects]

The use of antiviral drugs (lopinavir ritonavir and favipiravir) was separately approved by the Saitama Cardiovascular and Respiratory Center Ethics Committee. Regarding the management of personal information, the patient name was made anonymous so that the personal information could not be known. This study was a retrospective observational study and was approved by the hospital ethics committee (approval number 2019062).

[statistics]

Clinical data were expressed as the mean (standard deviation). JMP Ver.13, (SAS Institute Japan Co., Ltd., Tokyo) was used for the statistics. The comparison between different groups was performed using the Wilcoxon / Kruskal-Wallis test, and the cut-off value was determined by the ROC curve. The Spearman Rank test was used for testing the correlation. $P < 0.05$ was considered significant.

Result

Table 1 shows the patient background of the 28 patients with COVID-19. There were 3 in Group A, 5 in Group B, 10 in Group C and 10 in Group D. Although there was no significant difference in gender, there were many males in severe cases, and the average age increased and the complications (diabetes, chronic obstructive pulmonary disease, hypertension) tended to increase as the severity increased.

The history of smoking also tended to be higher in severe cases. The average time from the onset of symptoms to a negative RT-PCR was 19.9 days, about 10 days in the group without pneumonia, and about 20 days in the group with pneumonia who did not require treatment. It took about 28 days in the group that required anti-viral drugs.

The most common clinical symptoms (Table 2) were fever (78.5%) and cough (46.9%), and all cases who showed viral pneumonia on CT had fever and/or cough. Conversely, 4 out of 8 patients who did not have viral pneumonia on CT had neither cough nor fever. The only symptom that correlated with the severity was diarrhea, and there was also a significant difference between groups C and D. In group D, only 1 in 10 patients complained of dyspnea on admission, despite hypoxemia in all cases.

Stages	Total	A+B	C	D	P (total)	P (C vs D)
number	28	8(A,3 ; B,5)	10	10		
sex（M,%）	12 (42.8%)	4 (50.0%)	3 (30%)	5 (50.0%)	NS	NS
age	57.6 (15.5)	48.1 (21.6)	58.9 (14.2)	64.1 (5.2)	NS	NS
complications**	7 (33.3%)	0	3 (30%)	4 (40.0%)	NS	NS
Smoking history, yes	4 (19.1%)	0	1 (10%)	3 (30.0%)	NS	NS
RT-PCR positive days	19.9 (8.5)	9.8 (4.8)	19.9 (5.9)	28.2 (5.5)	0.0046	0.0321

*: mean±SD, **: diabetes、chronic obstructive pulmonary disease or hypertension

A denotes stage A, no symptoms; B, positive symptoms but no viral pneumonia on computed tomography (CT); C, positive symptoms and viral pneumonia on CT, but recovered without treatment; D, positive symptoms and viral pneumonia on CT and required anti-viral treatment.

Table 1. Patient Characteristics

Stages	Total	A+B	C	D	P (total)	P (C vs D)
Cough	13 (46.4%)	1 (12.5%)	6 (60%)	6 (60%)	NS	NS
Fever	22 (78.5%)	4 (50%)	9 (90%)	9 (90%)	NS	NS
Nasal discharge	2 (7.1%)	0	0	2 (20.0%)	NS	NS
Sore throat	6 (21.4%)	1 (12.5%)	3 (30%)	2 (20.0%)	NS	NS
Headache	8 (28.6%)	1 (12.5%)	4 (40%)	3 (30.0%)	NS	NS
Arthralgia	4 (14.3%)	2 (25.0%)	1 (10.0%)	1 (10.0%)	NS	NS
Muscle pain	4 (14.3%)	1 (12.5%)	1 (10.0%)	2 (20.0%)	NS	NS
Malaise	8 (28.6%)	3 (33.3%)	3 (30%)	2 (22.2%)	NS	NS
Anorexia	5 (17.8%)	0	3 (30%)	2 (20.0%)	NS	NS
Abdominal pain	1 (3.6%)	0	0	1 (10.0%)	NS	NS
Diarrhea	6 (21.4%)	0	1 (10%)	5 (50%)	0.0127	0.0437
Shortness of breath	1 (3.6)	0	0	1 (10.0%)	NS	NS

Table 2 . Symptoms

Stages	Total	A+B	C	D	P (total)	P (C vs D)
PaCO2 (torr)	36.5 (6.0)	37.5 (4.2)	38.7 (8.6)	34.5 (3.6)	NS	NS
PaO2 (torr)	75.5 (14.2)	94.9 (6.1)	78.9 (15.6)	66.3 (4.0)	NS	NS
WBC (/μL)	5,300 (2,007)	5,555 (2,506)	4,940 (1,368)	5,444 (2,224)	NS	NS
Lymphocyte (/μL)	1,246 (512)	1,566 (509)	1,300 (476)	833 (229)	0.0203	0.0401
D-dimer (μ/ml)	0.90 (0.49)	0.61 (0.06)	0.80 (0.29)	1.22 (0.65)	0.0246	NS
ALT (IU/L)	31.9 (18.2)	30.6 (10.1)	23.6 (11.8)	42.4 (25.5)	NS	NS
CK (IU/L)	121.8 (112.4)	145.6 (91.3)	72.2 (45.9)	155.9 (136.6)	NS	NS
CRP (mg/dL)	2.16 (4.34)	0.14 (0.10)	0.85 (0.84)	5.65 (6.51)	0.0005	0.0160
PCT (ng/mL)	0.05 (0.05)	0.03 (0.01)	0.03 (0.01)	0.11 (0.65)	NS	NS
ferritin (ng/mL)	518.9 (538.3)	207.0 (128.7)	282.1 (137.8)	950.8 (672.9)	0.0012	0.0019
KL-6 (U/mL)	209.4 (43.8)	163.5 (24.7)	217.3 (32.9)	211.8 (52.7)	NS	NS

Data are expressed mean (standard deviation).

Table 3. Laboratory data

Next, laboratory values (Table 3) correlated with severity were lymphocyte count, D-dimer, CRP, and ferritin. Among the cases with viral pneumonia, the laboratory values that showed significant differences between groups C and D were lymphocyte count, CRP, and ferritin. When the cut-off value for discriminating between the two groups was determined from the ROC curve, the lymphocyte count was 1,000/ μL or less, CRP was 4.16mg/dL or more, and ferritin was 434ng/mL or more. Of these, the upper limit of CRP in group C without treatment was 2.2 mg /dL. The lymphocyte count and the course of treatment (Fig. 1) showed that the initial lymphocyte count was 1,100/μL or less in all patients requiring treatment, and a tendency toward recovery was seen with treatment. Lymphocyte counts were ≥1,000/μL in 6 of 10 patients who improved without treatment despite viral pneumonia. In group B, the total amount was more than 1,200/μL in all five cases, and in group A, it was more than 1,900/μL in all three cases. Imaging findings (Table 4) showed that the frequency of single ground glass opacity, multiple ground glass opacity, crazy-paving, infiltration opacity increased, and the number of pneumonia zones increased according to the severity. The site of pneumonia was often found on the back of the lower lobe. The best distinction between groups C and D was the presence or absence of infiltrates. Based on the above, the five risk factors for COVID-19 pneumonia worsening were diarrhea, lymphocyte count of 1,000/μL or less, ferritin of 430ng/mL or more, CRP of 2.5mg/dL or more, and CT infiltration shadow. The number was 0 in group B, 1 or 2 in 60% of group C, and 2 or more in all cases in group D. The number of risk factors showed a strong correlation with the number of days from onset to negative PCR (Fig. 2, P = 0.0002).

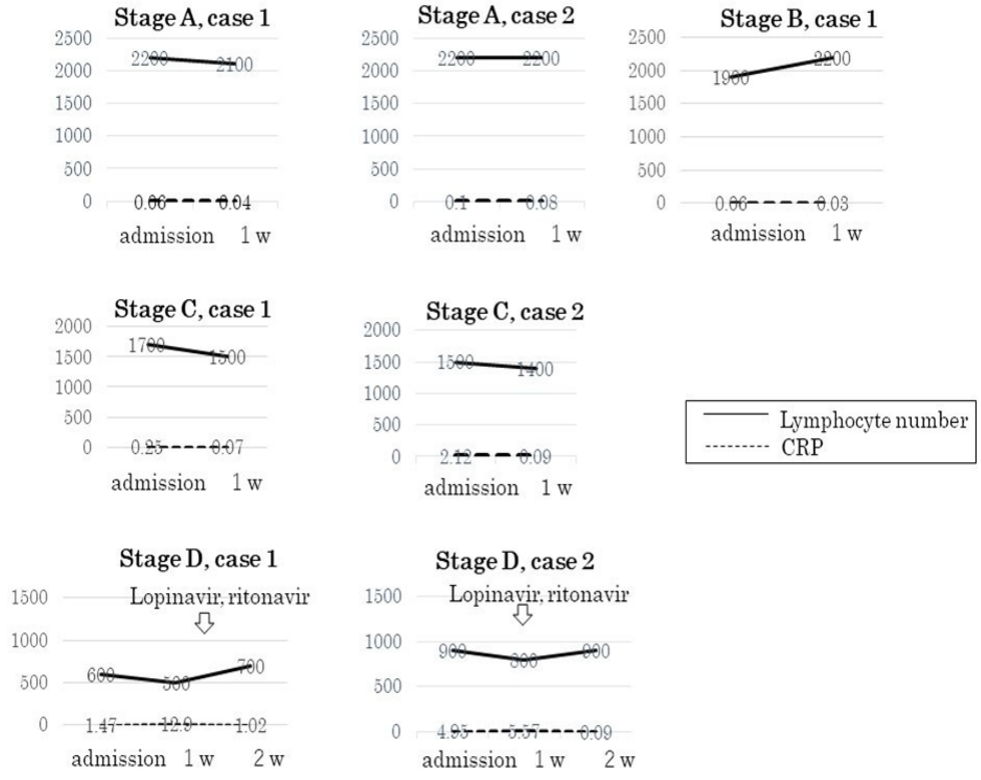

Fig. 1. Clinical courses of lymphocyte number and CRP

Stages	Total	C	D	P
number	20	10	10	
Single grand grass opacity	2 (10.0%)	2 (20%)	0	NS
Multiple grand grass opacities	18 (89.5%)	8 (80%)	10 (100%)	NS
Crazy-paving appearance	6 (30.0%)	1 (10%)	5 (50.0%)	0.0073
Consolidation	10 (52.6%)	1 (10%)	9 (90%)	<0.0001
Affected lung segments, n (SD)	9.2 (6.3)	4.8 (4.2)	13.6 (4.4)	0.0016

C denotes stage C, positive symptoms and viral pneumonia on computed tomography (CT), but recovered without treatment, or D, positive symptoms and viral pneumonia on CT and required anti-viral treatment.

Table 4. Finding of computed tomography

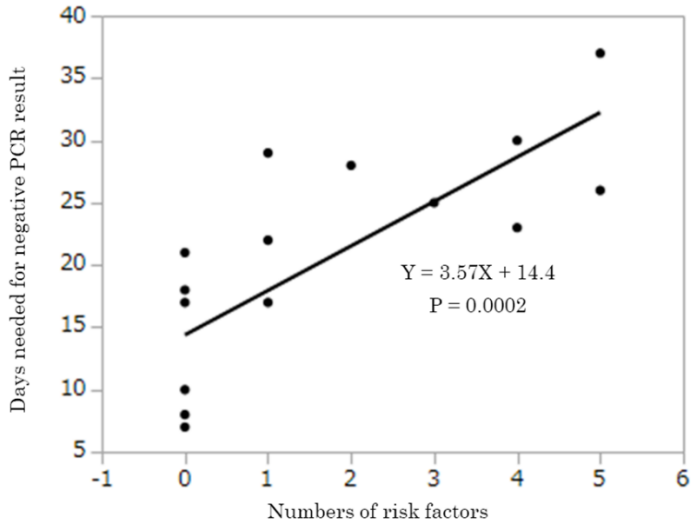

Fig. 2.
Numbers of risk factors and days from onset of symptoms to the negative result of RT-PCR for SARS-CoV2

Discussion

The specific and overall clinical features and imaging findings of some of the cases (14 Diamond Princess patients) presented in this study have been reported in a separate report (submitted), and here are related to treatment selection for useful clinical markers. When the antiviral drug is started after it has become severe, it is highly possible that the cytokine-storm progresses, leading to irreversible respiratory failure. However, lopinavir ritonavir and favipiravir, which are currently used for SARS-COV2, also have side effects [4, 5], and there is little evidence for their use in many cases of this disease, which is said to be naturally resolved in many cases. On the other hand, COVID-19 rapidly deteriorates from 10 days to 14 days after onset. Unlike influenza, which has a receptor on the upper respiratory tract mucosa [6], the receptor (ACE2) is mainly expressed in alveolar type II cells [7]. Therefore, the present virus has weak upper respiratory symptoms, and may become severe without notice and miss treatment. There was a patient admitted to our hospital from the Diamond Princess who had hypoxemia and widespread pneumonia even though the patient had not complained of shortness of breath, and was immediately treated in an intensive care unit. Identifying the risk factors for severe disease and start treatments if a patient has one of the risks before hypoxemia can be observed could reduce the number of patients who require mechanical ventilation. Figure 3 shows a private treatment strategy based on the ABCD assessment from the above viewpoints. The percentage of patients with positive findings in any of the five clinical markers shown in this

study were 57%, while the percentage of patients actually treated according to the Ministry of Health and Welfare guidelines were 36%. However, there are opinions that even very mild cases should be treated if the virus shedding period can be reduced, and further discussion is awaited. We would like to add some consideration to the five clinical markers shown in this study. According to reports from China, the poor prognostic factors were elderly, high SOFA score, and D-dimer ≥1μg/mL [8]. This study differs from the earlier study in examining factors of earlier severity, meaning pneumonia requiring treatment rather than death. Since SARS-CoV-2 has a receptor (ACE2) in the intestine as well as in the lung [9], diarrhea may indicate that the gastric fluid barrier has been broken. However, when evaluating diarrhea, it is necessary to carefully determine whether there are other factors that may cause diarrhea. In severe cases in China, diarrhea has been reported infrequently[10], and further accumulation of cases is necessary.

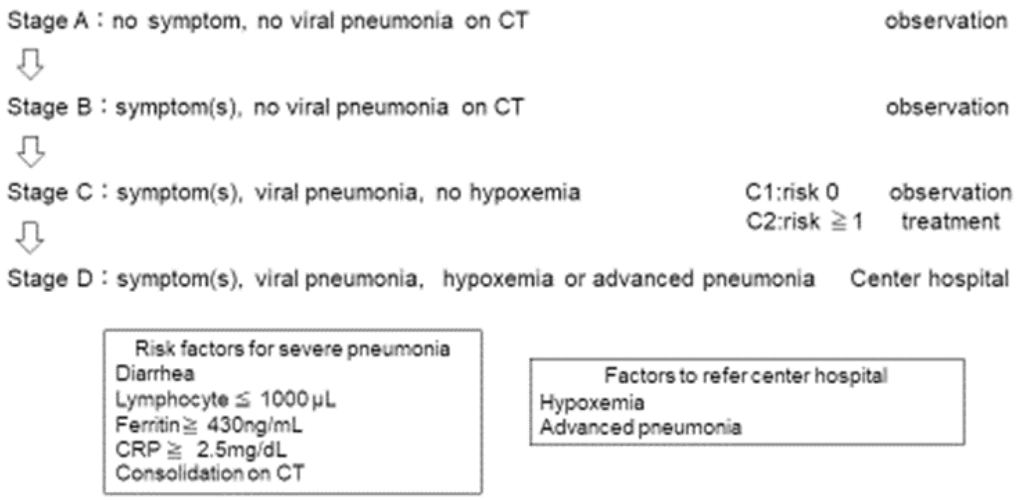

Fig. 3. ABCD assessment and COVID-19 treatment plan

It is reported that lymphocyte counts had decreased with increasing severity in Wuhan treatment guidelines, and autopsy findings indicate that lymph nodes are necrotic and the spleen is atrophied[11]. CRP was not elevated in mild COVID-19 in many cases, but increased in severe cases. However, procalcitonin, the same inflammatory marker, was not elevated in COVID-19 cases, including severe cases. Ferritin is one of the cytokine storm markers, but interestingly, it has been reported that it is not elevated in influenza A (H1N1pdm) [12]. In addition, a cytokine profile that increases with COVID-19 has already been reported[10]. It is known that CT images show ground-glass opacities on the dorsal side of the lower lobe, accompanied by a decrease in lung volume, and infiltration opacities increase as the disease becomes more severe[13]. In this study, the presence or absence of infiltrates was the simplest and most significant treatment criterion. Since SARS-CoV2 mainly targets alveolar type II cells, [7] it is easily speculated that surfactant production is impaired. Surfactant damage can be explained well by the decrease in alveolar volume due to increased surface tension of the alveoli and the dorsal ground-glass shadow due to the weighting effect of gravity. The crazy-paving findings that are common in this disease are also common in alveolar proteinosis in which the surfactant is impaired[14]. Finally, a strong correlation between the number of the five clinical markers and the time between onset and PCR-negativeness suggests that they may be used as quantitative variables that correlate with disease severity. In some ongoing clinical trials of antiviral drugs, the time until the negative result of the viral PCR may be an indicator, so the severity index presented here may also be useful for evaluation.

Since this study is a report on a small number of cases, it is necessary to further increase the cases and verify them. It has been reported that favipiravir, which is currently undergoing clinical trials, significantly reduces the SARS-CoV2 elimination period by the PCR method.[15] In such cases, treatment may be started earlier, while when vaccines may become practical the number of cases that can be followed up without treatment may increase.

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