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【 ORIGINAL ARTICLE 】

Clinical Features of 154 COVID-19 Patients and the Parameters for the Effective Detection of Pneumonia at the Time of the Initial Diagnosis in Japan

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Abstract:

Objective We aimed to clarify clinical and laboratory characteristics of coronavirus disease 2019 (COVID-19) patients, and further explore the features to detect COVID-19 pneumonia at the first visit to community-based hospitals.

Methods Diagnoses of COVID-19 were based on positive results from real-time reverse-transcription polymerase chain reaction testing of nasopharyngeal-swab specimens. We retrospectively reviewed the medical records of patients showing positive results. The clinical characteristics and results of blood tests were compared between the patients with and without pneumonia. The risk factors associated with pneumonia were then evaluated by a multivariable analysis.

Results The study cohort comprised 154 patients, including 117 patients (76.0%) with pneumonia at first visit. Significant differences were seen in age, the frequency of fever, tachycardia, desaturation (peripheral oxygen saturation ≤95%), any comorbidity, neutrocyte count and fraction, lymphocyte count and fraction, platelet count, lactate dehydrogenase (LDH), C-reactive protein (CRP), and fibrinogen between the patients with and without pneumonia. Using a multivariable analysis, CRP ≥0.3 mg/dL and fibrinogen >400 mg/dL were found to be associated with the presence of pneumonia.

Conclusion Community-based settings for screening COVID-19 patients should perform chest X-ray and blood tests for white blood cell fractions, fibrinogen, LDH, and CRP. Of these, elevations in the CRP and fibrinogen levels could be critically associated with the presence of COVID-19 pneumonia.

Key words: COVID-19, pneumonia, clinical feature, screening, CRP, fibrinogen

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Introduction

Since the first case of coronavirus disease 2019 (COVID-19) was identified in Wuhan, China in December 2019, the virus has spread worldwide. The World Health Organization declared a pandemic on March 4, 2020. In Japan, the first case of COVID-19 was confirmed on January 15, 2020, based on the Ministry of Health, Labor and Welfare (MHLW) announcement. As of June 3, 2020, a total of 16,986 cases of COVID-19 had been diagnosed under the State of Emergency covering all 47 prefectures in Japan, with 1,308 patients being hospitalized (1). As COVID-19 can lead acute respiratory distress syndrome (ARDS) at rates of 15-31% with an onset time of around 8-12 days (2), making a timely and accurate diagnosis while determining the individual risk of developing ARDS is important. In primary settings, the establishment of clinical and laboratory factors predicting and distinguishing asymptomatic patients, particularly those about to develop pneumonia would be useful. We have diagnosed 154 patients with COVID-19 at Tokyo Shinagawa Hospital, a community hospital located in

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the southern area of Tokyo, covering over 1,100,000 residents. The patients included were both those attending outpatient clinics with symptoms and asymptomatic subjects mainly identified due to close contact with already identified COVID-19 patients. This report could offer the first "real-world" data of COVID-19 patients from a community-based institution, and thus would support the general clinical practice and decision-making for potential COVID-19 patients in Japan. In the future, COVID-19 seems likely to be a major community-acquired pneumonia occurring throughout all seasons, so the analysis and classification of the patient characteristics at the time of initial diagnosis should prove valuable. Our findings provide information on the real features of COVID-19 patients diagnosed in a community hospital.

Materials and Methods

Study design and participants

This study was approved by the institutional review board and the need to obtain written informed consent was waived due to the retrospective nature of the investigation. Consecutive COVID-19 patients diagnosed in our institution from February 14 to April 30, 2020 were included for analysis. The diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was based on a positive result from real-time reverse-transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal-swab specimens at the public health center or an external laboratory. A blood sample and chest X-ray were obtained from each patient, and additional computed tomography (CT) was performed when abnormal findings were identified on X-rays. Medical records, chest X-ray and CT images were reviewed for the clinical findings. Epidemiological, demographic, clinical and laboratory data were extracted from electronic medical records. The normal ranges of laboratory data were based on institutional standards. Two researchers (MS and TS) independently reviewed the data collection forms to double-check the collected data.

Statistical analysis

Continuous variables are expressed as the median [interquartile range (IQR)] and number (%). The results for groups with pneumonia (Pneumonia group) and without pneumonia (Non-pneumonia group) were compared using the Mann-Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate. More precisely, the mean values of each laboratory parameter were compared using the Mann-Whitney *U* test and factors potentially associated with pneumonia were selected. Categorical classifications using the terms "within the normal limit" and "outside the normal limit" for each candidate were assessed using the χ^2 test or Fisher's exact test. To explore the risk factors associated with pneumonia, a univariable analysis was performed as dichotomous independent variables, using the following contrasts: age, ≥44 vs. <44 years (median for whole group); lactate dehydrogenase (LDH), ≥240 vs. <240 IU/L [based on the upper limit of the normal range (ULN)]; C-reactive protein (CRP), ≥0.3 vs. <0.3 mg/dL (based on ULN); fibrinogen, ≥400 vs. <400 mg/dL (based on ULN); Pulse, ≥100 vs. <100/min [based on the standard definition of tachycardia (3)]; Systolic blood pressure, ≥90 vs. <90 mmHg [based on the definition of the pneumonia severity scoring system CURB-65 (4)].

For all statistical analyses, values of $p<0.05$ were considered to be statistically significant. Near-significant predictors ($p<0.1$) of laboratory parameters were included in a stepwise multiple logistic regression analysis to identify significant independent predictors for the presence of pneumonia. All analyses were performed using the BellCurve for Excel 3.20 software program (Social Survey Research Information).

Results

Patients

The demographic and clinical characteristics of the patients are summarized in Table 1. We studied 154 consecutive patients (94 males, 61.0%: 60 females, 39.0%) with laboratory-confirmed SARS-CoV-2 infection. Median age was 44 years (IQR, 32-56 years), and 81.2% of patients (125/154) were ≤59 years old. No patients were pregnant. Of the total cohort, 113 patients (73.4%) first presented to our hospital on the fifth day after illness onset according to the guidelines issued by the MHLW for individuals showing fever or other symptoms. Pneumonia was present in 117 patients (76.0%) on the first visit. Figure shows the number of patients, the presence of pneumonia and the percentage of pneumonia among the patients, classified by days from onset until first visit. As shown, pneumonia could occur from the second day of illness. Pneumonia was confirmed in ≥50% of the patients who consulted ≥2 days after onset. Almost all patients (n=148; 96.1%) were able to attend our hospital independently, whereas the 6 remaining patients were brought by ambulance and required prehospital care due to pneumonia. Regarding the symptoms on presentation, 134 patients (87.0%) displayed fever ≥37.5℃, 103 patients (66.9%) had cough, and 83 patients (53.9%) had fatigue, thus representing the symptoms experienced by more than half of all patients. Our cohort included 23 desaturated patients [peripheral oxygen saturation (SpO_2) ≤95%, 14.9%], all of whom were in the Pneumonia group (p=0.0013, Table 1). Four patients who showed respiratory failure (SpO_2 ≤90%) on the first visit presented from 7 to 9 days after onset.

Other characteristics of age, pulse, fever, smell dysfunction, tachycardia, diabetes, and any comorbidity differed significantly between groups (Table 1). In brief, age (median, 48 years vs. 31 years; p<0.001), pulse (median, 92 beats/min vs. 84 beats/min; p=0.0056), frequency of fever (107/117, 91.5% vs. 27/37, 73.0%; p=0.0089), tachycardia (51/108, 47.2% vs. 6/31, 19.4%; p=0.0067), diabetes (13/117,

Table 1. Patient Demographics and Characteristics.

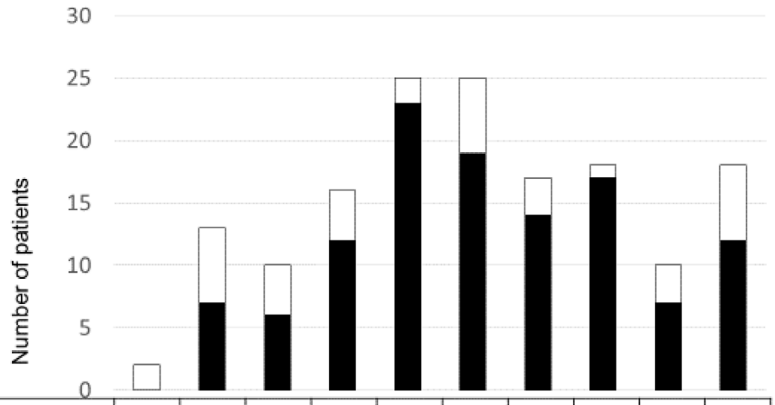
	Total (n=154)	Pneumonia (n=117)	Non pneumonia (n=37)	p
Age (years)	44 (32-56)	48 (37-59)	31 (26-36)	<0.001
Sex				0.3386
Female	60 (39.0%)	43 (36.8%)	17 (45.9%)	
Male	94 (61.0%)	74 (63.2%)	20 (54.1%)	
Time from illness onset (days)				
1-4	41 (26.6%)	25 (21.4%)	16 (43.2%)	
5-7	67 (43.5%)	56 (47.9%)	11 (29.8%)	
≥8	46 (29.9%)	36 (30.7%)	10 (27.0%)	
Walk-in	148 (96.1%)	111 (94.9%)	37 (100.0%)	0.3366
Ambulance	6 (3.9%)	6 (5.1%)	0 (0.00%)	
Presence of pneumonia	117 (76.0%)			
Fever	134 (87.0%)	107 (91.5%)	27 (73.0%)	0.0089
Cough	103 (66.9%)	77 (65.8%)	26 (70.3%)	0.6915
Fatigue	83 (53.9%)	62 (53.0%)	21 (56.8%)	0.7097
Dyspnea	28 (18.2%)	23 (19.7%)	5 (13.5%)	0.4718
Diarrhea/Nausea/Vomiting	39 (25.3%)	28 (23.9%)	11 (29.7%)	0.5180
Chest discomfort	28 (18.2%)	21 (17.9%)	7 (18.9%)	1.0000
Smell dysfunction	49 (31.8%)	32 (27.4%)	17 (45.9%)	0.0433
Taste dysfunction	55 (35.7%)	39 (33.3%)	16 (43.2%)	0.3260
Myalgia/Arthralgia	51 (33.1%)	39 (33.3%)	12 (32.4%)	1.0000
Headache	72 (46.8%)	50 (42.7%)	22 (59.5%)	0.0902
Current or ex-smoker	26 (16.9%)	17 (14.50%)	9 (24.30%)	0.2074
Pulse * (beats/min)	90 (80-102)	92 (82-102)	84 (73-92.5)	0.0056
Tachycardia (≥100 beats/min)	57 (41.0%)	51 (47.2%) (n=108)	6 (19.4%) (n=31)	0.0067
Systolic blood pressure (mmHg)**	121 (112-130)	120 (111-128.5)	123.5 (118-131.8)	0.1913
<90 mmHg	3 (2.0%)	3 (2.8%) (n=107)	0 (0.0 %) (n=30)	1.0000
Diastolic blood pressure (mmHg)**	78 (69-87)	77 (70-87)	80 (68.3-88.3)	0.7627
Desaturation (SpO_2≤95%)	23 (14.9%)	23 (19.7%)	0 (0.0%)	0.0013
Comorbidity	61 (39.6%)	53 (45.3%)	8 (21.6%)	0.0120
Hypertension	19 (12.3%)	17 (14.5%)	2 (5.4%)	0.2487
Respiratory disease	18 (11.7%)	15 (12.8%)	3 (8.1%)	0.5651
Diabetes	13 (8.4%)	13 (11.1%)	0 (0.0%)	0.0389
Hyperuricemia	11 (7.1%)	11 (9.4%)	2 (5.4%)	0.7349
Hyperlipidemia	6 (3.9%)	6 (5.1%)	0 (0.0%)	0.3366
Cardiac disease	5 (3.2%)	5 (4.3%)	0 (0.0%)	0.3379
Carcinoma	5 (3.2%)	4 (3.4%)	1 (2.7%)	1.0000
Other	7 (4.5%)	7 (6.0%)	0 (0%)	0.1973

*, **: Data were collected from 139 patients* or from 137 patients**.
Data are n (%) and median (IQR).

11.1% vs. 0/37, 0.0%; p=0.0389), and any comorbidity (53/117, 45.3% vs. 8/37, 21.6%; p=0.0120) were significantly higher in the Pneumonia group than in the Non-pneumonia group. The frequency of smell dysfunction was significantly lower in the Pneumonia group (32/117, 27.4%) than in the Non-pneumonia group (17/37, 45.9%; p=0.0433).

Laboratory findings

Laboratory findings at the first visit are summarized in Table 2, showing that white blood cell (WBC) fractions, platelet count, and several serum parameters were significantly more frequently abnormal in the Pneumonia group than in the Non-pneumonia group. Our cohort, especially the Pneumonia group, showed reduced lymphocyte counts and platelet counts, but normal WBC counts. Briefly, leucopenia (WBC count <3.5×10^9/L) was present in 36 patients overall (23.4%) but it was significantly more frequent in the Non-pneumonia group (p=0.0072). Instead, the neutrocyte count (p=0.043) and neutrocyte fraction (p<0.001) were relatively increased (but within normal ranges), while the lymphocyte count (p<0.001) and lymphocyte fraction (p< 0.001) were significantly decreased in the Pneumonia group. The platelet count was significantly lower in the Pneumonia group (p=0.0034). As for the serum parameters, the LDH, CRP and fibrinogen levels were significantly higher in the Pneumonia group than in the Non-pneumonia group (p<



Days from onset of illness	1	2	3	4	5	6	7	8	9	10~
Number of patients	2	13	10	16	25	25	17	18	10	18
Pneumonia	0	7	6	12	23	19	14	17	7	12
Non-pneumonia	2	6	4	4	2	6	3	1	3	6
Ratio of patients with pneumonia (%)	0	53.8	60.0	75.0	92.0	76.0	82.4	94.4	70.0	66.7

Figure. **The number of patients with and without pneumonia at first visit and the number of days from the onset of illness. The bars represent the number of patients with pneumonia (black) and non-pneumonia (white). Pneumonia was seen on the second day from symptoms onset and consistently presented in 50% or more of patients of each day after that.**

Table 2. **Laboratory Findings.**

	Total (n=154)	Pneumonia (n=117)	Non-pneumonia (n=37)	p
WBC,×10^9/L	4.3 (3.7-5.4)	4.3 (3.8-5.3)	4.5 (3.6-5.5)	0.9899
<3.5	36 (23.4%)	21 (17.9%)	15 (40.5%)	0.0072
3.5-8	116 (75.3%)	94 (80.3%)	22 (59.5%)	0.0155
>8	2 (1.3%)	2 (1.7%)	0 (0.00%)	1.0000
Neutrocytes,×10^9/L	2.79 (2.15-3.63)	2.85 (2.39-3.75)	2.44 (1.84-3.33)	0.043
≤2.0	29 (18.8%)	27 (23.1%)	12 (32.4%)	0.2813
Neutrocyte fraction, %	64.8 (58.0-72.6)	66.3 (61.8-73.9)	58.1 (46.5-66.0)	<0.001
<40	4 (2.6%)	1 (0.9%)	3 (8.1%)	0.0433
≥80	11 (7.1%)	10 (8.5%)	1 (2.7%)	0.4623
Lymphocytes,×10^9/L	1.07 (0.80-1.42)	1.01 (0.77-1.27)	1.30 (0.97-1.76)	0.0021
<1.0	63 (40.9%)	57 (48.7%)	6 (16.2%)	<0.001
Lymphocyte fraction, %	26.1 (19.4-31.4)	24.7 (18.6-29.3)	31.4 (23.6-41.5)	<0.001
<25	65 (42.2%)	55 (47.0%)	10 (27.0%)	0.0366
≥45	8 (5.2%)	1 (0.9%)	7 (18.9%)	<0.001
Platelets,×10^9/L	18.8 (15.1-22.6)	18.0 (14.6-21.9)	21.9 (17.9-24.3)	0.0034
<15	32 (20.8%)	27 (23.1%)	5 (13.5%)	0.2520
LDH, U/L	203.5 (174.3-262.8)	224 (190-288)	170 (148-198)	<0.001
>240	53 (34.4%)	52 (44.4%)	1 (2.7%)	<0.001
CRP, mg/dL	1.21 (0.31-3.48)	2.16 (0.83-4.26)	0.16 (0.06-0.30)	<0.001
<0.3	36 (23.4%)	8 (6.8%)	28 (75.7%)	<0.001
0.3-<5	82 (53.3%)	73 (62.4%)	9 (24.3%)	
5-10	19 (12.3%)	19 (16.2%)	0 (0.0%)	<0.001
>10	7 (4.6%)	7 (6.0%)	0 (0.0%)	
Fibrinogen, mg/dL *	395 (324-482)	434 (355.3-528.8)	276.5 (230-330.8)	<0.001
>400	52 (33.8%)	51 (54.3%)	1 (3.6%)	<0.001
D-dimer, μg/L **	0.3 (0.1-0.55)	0.3 (0.1-0.7)	0.1 (0.1-0.4)	0.0773
≥1.0	19 (12.3%)	16 (16.8%)	3 (10.7%)	0.5597

*, **: Data were collected from 122 patients* or from 123 patients**

Data are given as n (%) or median (IQR).

WBC: white blood cell, LDH: lactate dehydrogenase, CRP: C-reactive protein

p values comparing Pneumonia and Non-pneumonia are from the Mann-Whitney *U* test, χ^2, or Fisher's exact test.

Table 3. **Uni- and Multivariable Analyses of Odds Ratio for Pneumonia.**

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	p
Age ≥44 years	3.881	1.720-8.757	0.0011			
Fever≥37.5 °C	4.115	1.551-10.918	0.0045			
Tachycardia≥100 beats/min	2.026	0.762-5.387	0.1573			
Lymphocyte count<1.0 ($\times10^9$/L)	2.246	1.016-4.961	0.0455			
Lymphocyte fraction<25%	2.842	1.263-6.396	0.0116	0.8053	0.233-2.779	0.7318
LDH ≥240 U/L	15.000	3.447-65.276	<0.001	0.7788	0.116-5.221	0.7968
CRP ≥0.3 mg/dL	26.0182	10.013-67.608	<0.001	0.0760	0.022-0.260	<0.001
Fibrinogen>400 mg/dL	41.595	5.417-319.367	<0.001	0.0764	0.008-0.696	0.0225

OR: odds ratio, CI: confidence interval

0.001).

Uni- and multivariable analyses of Pneumonia and Non-pneumonia groups

Based on the differences between the Pneumonia and Non-pneumonia groups (Table 1, 2), we assessed age, fever, tachycardia, lymphocyte counts, lymphocyte fraction (%), LDH, CRP, and fibrinogen by univariable analyses for the risk of developing pneumonia (Table 3). Of these, a higher age, febrile status, lymphocytopenia, increased LDH, increased CRP and increased fibrinogen were associated with pneumonia. We therefore further analyzed 122 patients with complete data for all variables (94 Pneumonia patients, 28 Non-pneumonia patients) in the multivariable logistic regression model for lymphocyte fraction, LDH, CRP and fibrinogen. Among the 4 candidate factors, elevated CRP ≥0.3 mg/dL and fibrinogen >400 mg/dL were associated with the presence of pneumonia (p<0.001, p=0.0225, respectively) (Table 3).

Discussion

This retrospective case-control study revealed the clinical features at the first visit for patients diagnosed with SARS-CoV-2 infection at a community-based hospital in Japan. Several reports on COVID-19 have concerned the clinical features and clinical and laboratory characteristics associated with severity of illness (5-7). Thus, this study focused on the characteristics at first visit and performed a cross-sectional extraction of factors contributing to the detection of pneumonia from clinical characteristics, including laboratory findings. In our study cohort, most patients were young, similar to the patient characteristics of representative reports from Wuhan, China (5, 8). In Japan, particularly in urban areas such as Tokyo, COVID-19 clusters were detected from a houseboat, dinner parties, a trade exhibition in a conference hall and live music concerts in clubs (9), and many young individuals seemed to be infected. Most patients followed the guidelines issued by MHLW and visited the hospital more than 5 days after onset, but some cases were seen in which pneumonia was evident in patients from 2 days after onset (Figure).

As a recent report mentioned that SARS-CoV-2 virus could enter cells by binding to angiotensin-converting enzyme (ACE)2, which is highly expressed in nasal epithelial cells and alveolar type 2 epithelial cells (10), pneumonia could occur in the early phase without symptoms (11). It has been reported that although the bulk of patients only experienced mild symptoms such as nasal congestion, cough, and sore throat, approximately 15-20% showed a deterioration which developed into severe pneumonia (12) and clinically worsened patients typically show dyspnea at days 4-10 after onset (5). In our cohort, all patients who had respiratory failure at the first visit had had 7 days or more after the onset. Additionally, pneumonia was already confirmed in 75% of the patients who presented to the hospital within 7 days after onset (Figure). Therefore, patients who have pneumonia at first visit should be diagnosed as soon as possible within 7 days after onset prior to developing severe status and need to be monitored carefully.

Laboratory findings showed that no COVID-19 patients with or without pneumonia displayed WBC counts >9.0×10^9/L. WBC counts have also been reported as significantly lower in COVID-19 patients confirmed by RT-PCR (13), and another report noted that leukocytosis (irrespective of whether it represented neutrophilia, lymphocytosis, or both) was rare among COVID-19 patients (14). Rather, leukocytosis is thought to suggest the presence of a bacterial infection, superinfection (14, 15), acute exacerbation of interstitial pneumonitis (16) or another viral pneumonia such as by influenza virus (17), all of which need to be differentiated from COVID-19 pneumonia.

Our study showed the plasma levels of CRP and fibrinogen levels to be useful markers to detect COVID-19 pneumonia. A recent report mentioned that the plasma CRP level correlated positively with the severity of COVID-19 pneumonia (18). In our study, an elevated CRP level at the initial examination was useful for detecting pneumonia. The plasma levels of fibrinogen are known to be elevated in inflammatory diseases (19, 20). COVID-19 has also been reported to induce coagulopathy with prominent elevations of D-dimer and fibrin/fibrinogen degradation products (8, 21-23). Previous reports mentioned the utility of fibrinogen or D-dimer as factors associated with an aggravated severity of

disease. This study revealed a significant increase in fibrinogen at the first visit. An elevated fibrinogen concentration at the first visit might offer a useful predictor of the presence of pneumonia in the early phase of COVID-19.

Comparisons of the patient characteristics and laboratory findings between Pneumonia and Non-pneumonia groups at first visit revealed an older age, febrile status, tachycardia, diabetes as a comorbidity, high neutrocyte fraction, lymphopenia, and high levels of CRP, LDH, and fibrinogen as potentially useful factors associated with pneumonia. When these findings are seen, chest CT is recommended. Surprisingly, 76.0% of the patients already had pneumonia on presentation, 10% of whom did not have a fever and presented to the hospital mostly because they had been in close contact with a known COVID-19 patient. Considering that some patients are asymptomatic, blood testing is warranted for screening. Taken together with these findings, COVID-19 pneumonia could be detected in community-based primary settings by not only chest X-rays, but also blood testing, including WBC fractions and the concentrations of fibrinogen, LDH, and CRP.

Limitations

This study is associated with several limitations. First, this study was conducted at a single-center hospital with a limited sample size. Second, owing to medical resources at first visit, the clinical course over time was not taken into account. Third, because a CT scan was performed when pneumonia was suspected on chest X-rays, extremely minor pneumonia could be excluded. We believe that including the clinical course in the analysis of characteristics at first visit will shed light on the pathology of COVID-19 in the future.

Conclusion

In conclusion, community-based settings for screening COVID-19 patients, including asymptomatic cases, should perform chest X-rays and blood tests for WBC fractions, fibrinogen, LDH, and CRP. Of these, high concentrations of CRP and fibrinogen may be critically associated with COVID-19 pneumonia.

The authors state that they have no Conflict of Interest (COI).

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