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

Miwa Morikawa¹, Masahiro Shinoda¹, Shinichiro Ota¹, Yuto Yoshida¹, Takatomo Hirouchi¹, Kanako Shinada¹, Osamu Sasaki², Takashi Sato¹, Kenichi Kamachi³ and Masaharu Shinkai¹

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

(Intern Med 60: 31-37, 2021)
(DOI: 10.2169/internalmedicine.5528-20)
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, \( \chi^2 \) 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 \( \chi^2 \) 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)].

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°C, 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 (SpO2) ≤95%, 14.9%], all of whom were in the Pneumonia group (p=0.0013, Table 1). Four patients who showed respiratory failure (SpO2 ≤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,
than in the Non-pneumonia group. Our cohort, especially significantly more frequently abnormal in the Pneumonia group. The platelet count was significantly lower in the Pneumonia group (p=0.043) and neutrocyte fraction (p<0.001) were relatively increased (but within normal ranges), while the lymphocyte count (p=0.0072). Instead, the neutrocyte overall (23.4%) but it was significantly more frequent in the Non-pneumonia group than in the Pneumonia group. The frequency of smell dysfunction was significantly higher in the Pneumonia group than in the Non-pneumonia group (p=0.0433). As for the serum parameters, the LDH, lymphocyte count (p<0.001) and lymphocyte fraction (p<0.001) were significantly decreased in the Pneumonia group. CRP and fibrinogen levels were significantly higher in the Pneumonia group than in the Non-pneumonia group. The 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 than in the Non-pneumonia group (p<

### 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  |
| Female                   | 60 (39.0%)   | 43 (36.8%)       | 17 (45.9%)           | 0.3386  |
| 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 (0.0%)             |         |
| 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  |
| Snell 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 (14.5%)       | 9 (24.3%)            | 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%)       | 6 (19.4%)            | 0.0067  |
| Systolic blood pressure** (mmHg) |           |                  |                      |         |
| <90 mmHg                 | 121 (112-130)| 120 (111-128.5) | 123.5 (118-131.8)    | 0.1913  |
|                          | 3 (2.0%)     | 3 (2.8%)         | 0 (0.0%)             | 1.0000  |
| Diastolic blood pressure** (mmHg) |       |                  |                      |         |
| ≥90 mmHg                 | 78 (69-87)   | 77 (70-87)       | 80 (68-88.3)         | 0.7627  |
| Desaturation (SpO₂≤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%)             | 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
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             |               |                   |                      |      |
| <3.5                    | 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|
| Neutrophils,×10^9/L     |               |                   |                      |      |
| ≤2.0                    | 2.79 (2.15-3.63) | 2.85 (2.39-3.75) | 2.44 (1.84-3.33)     | 0.043 |
| Neutrophil fraction, %  |               |                   |                      |      |
| <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     |               |                   |                      |      |
| ≤1.0                    | 1.07 (0.80-1.42) | 1.01 (0.77-1.27) | 1.30 (0.97-1.76)     | 0.0021|
| Lymphocyte fraction, %  |               |                   |                      |      |
| <25                     | 63 (40.9%)    | 57 (48.7%)        | 6 (16.2%)            | <0.001|
| ≥45                     | 26.1 (19.4-31.4) | 24.7 (18.6-29.3) | 31.4 (23.6-41.5)     | <0.001|
| Platelets,×10^9/L       |               |                   |                      |      |
| ≤15                     | 18.8 (15.1-22.6) | 18.0 (14.6-21.9) | 21.9 (17.9-24.3)     | 0.0034|
| LDH, U/L                | 203.5 (174.3-262.8) | 224 (190-288) | 170 (148-198)        | <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|
| Fibrinogen, mg/dL *     | 395 (324-482) | 434 (355.3-528.8) | 276.5 (230-330.8)    | <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, χ², or Fisher’s exact test.
days after onset (Figure). 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 >9.0x10^9/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 COVID-19 pneumonia.

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

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 neutocyte 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).

References

1. Ministry of Health LaW. Latest information on Coronavirus disease 2019 2020 [Internet]. [cited 2020 Jun 3]. Available from: http s://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000164708_00001.ht m#kokunaihassei (in Japanese)

2. Li X, Ma X. Acute respiratory failure in COVID-19: is it “typical” ARDS? Crit Care 24: 198, 2020.

3. Heart rate. e-healthnet. Ministry of Health, Labour and Welfare [Internet]. [cited 2020 Jun 3]. Available from: https://www.e-health net.mhlw.go.jp/information/dictionary/exercise/ys-032.html (in Japanese)

4. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58: 377-382, 2003.

5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507-513, 2020.

6. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 369: m1966, 2020.

7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1045-1054, 2020.

8. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 133: 1032-1038, 2020.

9. Furuse Y, Ko YK, Saito M, et al. Epidemiology of COVID-19 outbreak in Japan, January-March 2020. Jpn J Infect Dis 10: 7883, 2020.

10. Sungnak W, Huang N, Bécanin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 26: 681-687, 2020.

11. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 15: 700-704, 2020.

12. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323: 1061-1069, 2020.

13. Mardani R, Ahmadi Vasmehjani A, Zali F, et al. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR: a diagnostic accuracy study. Arch Acad Emerg Med 8: e43, 2020.

14. Frater JL, Zini G, d’Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol 42 (Suppl 1): 11-18, 2020.

15. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med 58: 1063-1069, 2020.

16. Enomoto N, Oyama Y, Enomoto Y, et al. Differences in clinical features of acute exacerbation between connective tissue disease-associated interstitial pneumonia and idiopathic pulmonary fibrosis. Chron Respir Dis 16: 1479972318809476, 2019.

17. Jain S, Benoit SR, Skarininski J, Bramley AM, Finelli L; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Influenza-associated pneumonia among hospitalized patients with 2009 pandemic influenza A (H1N1) virus-United States, 2009. Clin Infect Dis 54: 1221-1229, 2012.

18. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob 19: 18, 2020.

19. Danik JS, Paré G, Chasman DI, et al. Novel loci, including those related to Crohn disease, psoriasis, and inflammation, identified in the Women’s Genome Health Study. Circ Cardiovasc Genet 6: 134-141, 2009.

20. Lind L. Circulating markers of inflammation and atherosclerosis. Atherosclerosis 169: 203-214, 2003.

21. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 135: 2033-2040, 2020.

22. Fogarty H, Townsend L, Ni Chealáigh C, et al. COVID19 coagulopathy in Caucasian patients. Br J Haematol 189: 1044-1049, 2020.

23. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180: 1-11, 2020.
