

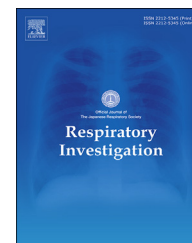


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## Original article

# Diagnostic prediction of COVID-19 based on clinical and radiological findings in a relatively low COVID-19 prevalence area



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## ABSTRACT

**Background:** Distinguishing coronavirus disease 2019 (COVID-19) pneumonia from other lung diseases is often difficult, especially in a highly comorbid patient population in a low prevalence region. We aimed to distinguish clinical data and computed tomography (CT) images between COVID-19 and other lung diseases in an advanced care hospital.

**Methods:** We assessed clinical characteristics, laboratory data, and chest CT images of patients with COVID-19 and non-COVID-19 patients who were suspected of having COVID-19 between February 20 and May 21, 2020, at the University of Tokyo Hospital.

**Results:** Typical appearance for COVID-19 on CT images were found in 24 of 29 COVID-19 cases and 21 of 168 non-COVID-19 cases, according to the Radiological Society of North America Expert Consensus Statement (for predicting COVID-19, sensitivity 0.828, specificity 0.875, positive predictive value 0.533, negative predictive value 0.967). When we focused on cases with typical CT images, loss of taste or smell, and close contact with COVID-19

**Abbreviations:** COVID-19, coronavirus disease 19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; RT-PCR, reverse transcription-polymerase chain reaction; CT, computed tomography; RSNA, Radiological Society of North America; CRP, C-reactive protein; Cov19Neg, negative for pneumonia; Cov19Aty, atypical appearance; Cov19Ind, indeterminate appearance; Cov19Typ, typical appearance; WBC, white blood cell; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; ACE2, angiotensin-converting enzyme 2.

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Fibrinogen  
White blood cell count

patients were exclusive characteristics for the COVID-19 cases. Among laboratory data, high fibrinogen ( $P < 0.01$ ) and low white blood cell count ( $P < 0.01$ ) were good predictors for COVID-19 with typical CT images in multivariate analysis.

**Conclusions:** In a relatively low prevalence region, CT screening has high sensitivity to COVID-19 in patients with suspected symptoms. When chest CT findings are typical for COVID-19, close contact, loss of taste or smell, lower white blood cell count, and higher fibrinogen are good predictors for COVID-19.

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## 1. Introduction

The outbreak of coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in December 2019. Since then, it has rapidly spread around the world. As of January 31, 2021, the World Health Organization (WHO) reported a total of 102 million cases globally, with an average mortality of 2.2% [1]. However, the disease prevalence varies across countries and regions. In Tokyo, Japan, the prevalence is relatively low, at 12 cases per million people per day on May 1, 2020, compared to that in high prevalence areas, such as in New York, USA, at 99 cases per million, and in Lombardia, Italy, at 73 cases per million on the same day.

Timely diagnosis of COVID-19 is of critical importance not only for patients but also for infection control in medical facilities. The gold standard for diagnosis is the detection of SARS-CoV-2 using antigen test or reverse transcription-polymerase chain reaction (RT-PCR). However, it may produce false-negative results [2] and turnaround time may be long [3] because most RT-PCR tests are performed outside the hospital.

Other than the microbiological test, clinical characteristics, laboratory data, and computed tomography (CT) imaging are useful for diagnosis. Chest CT imaging plays an important role in the diagnosis and evaluation of the disease for several reasons: Typical imaging features of COVID-19 were reported to have high sensitivity especially in high prevalence regions [4], CT findings are correlated with disease severity [5], and imaging evaluation can be performed on time. Classifications of chest CT images related to COVID-19, such as Radiological Society of North America (RSNA) Expert Consensus Statement [6], CO-RADS [7], and COVID-RADS [8], and their diagnostic value have been reported. While many national and international organizations do not recommend CT as a routine screening tool for COVID-19 [9,10], CT imaging is an important diagnostic aid where CT examination is easily accessed.

Clinical characteristics of COVID-19 are different from other community-acquired infections to some extent. Other than common symptoms of respiratory infection, one of the unique symptoms is the alteration of smell or taste, reported in about 30–60% of patients [11–13] and can be a clue to the diagnosis [14,15]. Typical laboratory findings that have been reported are lymphopenia and increase of ferritin, D-dimer, and C-reactive protein (CRP), some of which are predictive for disease severity [16–19].

Prediction models for the diagnosis or prognosis have already been proposed [20]. However, many diagnostic predictions were made for patients without severe comorbidities visiting the emergency room in a high prevalence area [21]. Thus, most non-COVID-19 patients in these studies were diagnosed with other community-acquired infections. On the other hand, in low prevalence areas and an advanced care hospital, the pre-test probability of COVID-19 is low and various infectious and non-infectious diseases need to be distinguished from COVID-19 promptly and appropriately in order not to delay the treatment of these diseases. In the present study, we aimed to reveal how well clinical characteristics, laboratory data, and CT images according to RSNA Expert Consensus Statement could help distinguish COVID-19 from other lung diseases in advanced care hospitals where visiting patients have many comorbidities.

## 2. Patients and methods

### 2.1. Ethical approval

This single-center retrospective comparative study was conducted with the approval of the Institutional Ethics Committee of the University of Tokyo (2020094NI, approved on June 22, 2020) and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was waived due to the retrospective nature of the study. The privacy of all patients was protected.

### 2.2. Study population

Patients with one or more symptoms suggestive of COVID-19 (fever ( $\geq 37.5$  °C), cough, dyspnea, tachypnea, malaise, hypoxemia) on admission at The University of Tokyo Hospital were reported by their attending physicians to our dedicated COVID-19 team, consisting of pulmonologists and infectious disease specialists for COVID-19 control. Consecutive cases that were reported between February 20 and May 21, 2020, were included in the study. Patients who were hospitalized for more than 2 weeks upon symptom onset, who were younger than 20 years, or had no RT-PCR or CT examination performed, were excluded. Patients who were diagnosed with COVID-19 in other medical facilities and admitted to our hospital in this period were also included in the study.

Patients were classified either as COVID-19 or non-COVID-19 according to the RT-PCR results. RT-PCR for the detection of

SARS-CoV-2 from nasopharyngeal or sputum samples was performed using LightMix® Modular SARS and Wuhan CoV E-gene kit (TIB Molbiol, Berlin, Germany) and LightMix® Modular Wuhan CoV RdRP-gene kit (TIB Molbiol) with Light-Cycler Multiplex RNA Virus Master (Roche, Basel, Switzerland) according to the manufacturer's instructions [22]. Patients with a high index of clinical suspicion underwent testing on RT-PCR multiple times at the discretion of the dedicated team.

### 2.3. CT image interpretation

The CT findings were classified by three board-certified diagnostic radiologists (6-, 7-, and 13-year experience of chest radiology), as negative for pneumonia (Cov19Neg), atypical appearance (Cov19Aty), indeterminate appearance (Cov19-Ind), and typical appearance (Cov19Typ), according to RSNA Expert Consensus Statement on Reporting Chest CT Findings [6] (Fig. 1A–D). All three observers were blinded to the clinical information, including RT-PCR results. Each observer independently scored the CT images, and the final diagnosis was decided by the majority. If there were total disagreements among the observers, the final diagnosis was decided by consensus.

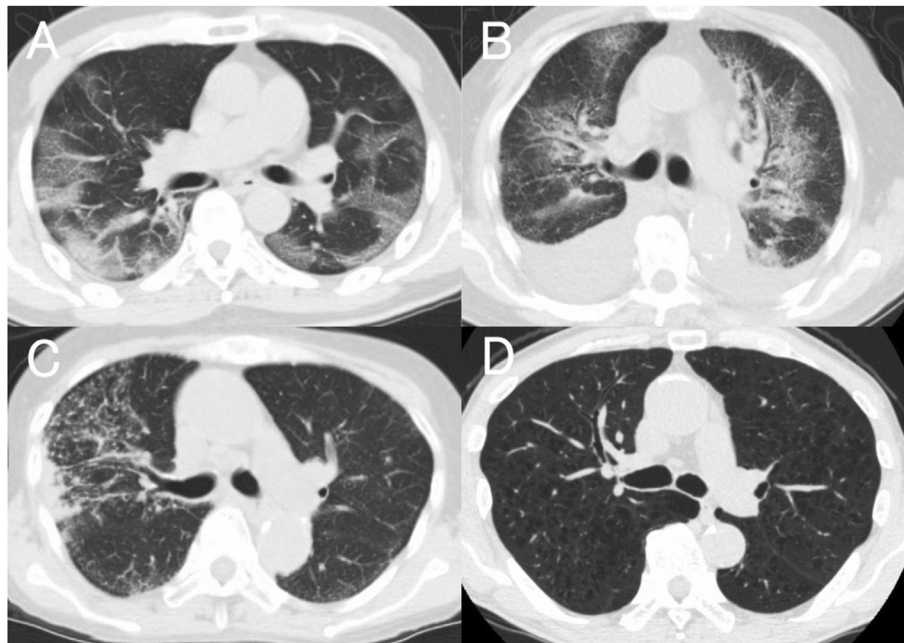
Since we found only a few cases of COVID-19 whose CT images were classified as other than Cov19Typ in our study population, statistical analysis of clinical data comparing COVID-19 with non-COVID-19 was considered inappropriate in cases without Cov19Typ images. Thus, clinical data presented below was reviewed and analyzed only in cases with Cov19Typ CT images.

### 2.4. Clinical data

The clinical characteristics, laboratory data, and chest CT images extracted from the patient medical records were reviewed retrospectively. We focused on demographic data, smoking history, underlying comorbidities, symptoms and signs, duration from onset of symptoms to CT, and laboratory data around the day that CT examination was performed. Symptoms including the loss of taste or smell were based on voluntary reporting.

### 2.5. Statistical analysis

Statistical analysis was conducted using R software (R version 3.6.3, The R Foundation for Statistical Computing, Vienna, Austria). For CT images, the overall agreement was quantified using Fleiss' kappa calculated across observers. For clinical and laboratory data, the comparisons of quantitative variables were evaluated using a non-paired *t*-test or Mann–Whitney *U* test according to the normality of data assessed by the Shapiro–Wilk test. The categorical data were evaluated using the Pearson  $\chi^2$  test or Fisher's exact test. Multivariate analysis was performed using binomial logistic regression analysis with the case wise deletion method for missing values. Variables were selected based on the stepwise method and existing knowledge of clinical meaning; lactate dehydrogenase, C-reactive protein, and fibrinogen as markers of inflammation, D-dimer as a marker of blood coagulation, aspartate aminotransferase, and white blood cell (WBC) count according to previous reports of COVID-19 [16,23]. In addition,



**Fig. 1** – Typical images for each CT finding category of RSNA Expert Consensus Statement [6]. A: Cov19Typ is characterized mainly by peripheral, bilateral ground-glass opacity, or findings of organizing pneumonia. B: Cov19Ind is characterized mainly by diffuse, perihilar, or unilateral ground-glass opacity. C: Cov19Aty is characterized mainly by isolated consolidation, discrete small nodules, lung cavitation, or smooth interlobular septal thickening with pleural effusion. D: Cov19Neg is characterized by no CT features to suggest pneumonia. Abbreviations: CT, computed tomography.



age and sex were included as general variables. The receiver operating characteristic (ROC) curve for COVID-19 was made according to the results of binomial logistic regression analysis. All *P*-values corresponded to two-sided tests. Statistical significance level set was set at  $P < 0.05$ .

### 3. Results

#### 3.1. Classification of CT images

We enrolled 287 patients who were reported to our dedicated COVID-19 team between February 20 and May 21, 2020. Ninety patients were excluded because they had been hospitalized for more than 2 weeks upon symptom onset ( $n = 9$ ), were younger than 20 years ( $n = 5$ ), had no RT-PCR or CT examination performed ( $n = 72$  and  $n = 4$ , respectively). Thus, we included 197 cases (COVID-19, 29 cases; non-COVID-19, 168 cases) in the present study.

The CT findings were scored by three radiologists. Kappa value was good, especially for Cov19Typ (Kappa value for whole cases, 0.634 [95% CI, 0.584–0.684]; Cov19Typ, 0.750 [0.670–0.831]; Cov19Ind, 0.614 [0.533–0.695]; Cov19Aty, 0.541 [0.461–0.622]; Cov19Neg, 0.648 [0.567–0.728]). At least two of the three radiologists agreed on a CT classification in every case. Cov19Typ were more likely seen in COVID-19 cases than other CT findings compared with non-COVID-19 cases ( $P < 0.01$ , Fisher's exact test). In fact, in most COVID-19 cases, CT images were classified as Cov19Typ. In contrast, about half of the cases with Cov19Typ images were non-COVID-19 (Table 1). This means that Cov19Typ CT images had high sensitivity but low PPV. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Cov19Typ findings for COVID-19 were 0.828 [95% CI, 0.642–0.942], 0.875 [0.815–0.921], 0.533 [0.379–0.683], and 0.967 [0.925–0.989], respectively. Some examples of confusing cases were shown in Fig. 2 (non-COVID-19 cases with Cov19Typ, Fig. 2A–B; COVID-19 cases with other than Cov19Typ, Fig. 2C–D).

#### 3.2. Clinical characteristics of Cov19Typ cases

Of 45 cases with Cov19Typ images, 24 were COVID-19 and 21 were non-COVID-19. The final diagnosis of non-COVID-19 cases ranged from infectious diseases to non-infectious diseases (Table 2) and 2 non-COVID-19 cases did not reach a final diagnosis. Clinical characteristics were different between COVID-19 and non-COVID-19 cases (Table 3). Especially, loss of taste or smell and close contact with COVID-19 patients were exclusive characteristics for our COVID-19 cases. Among laboratory data, multivariate analysis revealed that increased

fibrinogen and low level of WBC count were related to COVID-19 (Table 4). Lymphocytopenia and D-dimer levels, previous predictors for COVID-19, were similar between COVID-19 and non-COVID-19. The area under the ROC curve for COVID-19 was 0.866 [95% CI, 0.745–0.988] (Fig. 3), which means higher fibrinogen and lower WBC count were good predictors for COVID-19 in cases with Cov19Typ images.

#### 3.3. Examples of COVID-19 without typical CT findings

Among 29 cases of COVID-19, 5 cases of CT findings were not typical (Cov19Neg, 2; Cov19Aty, 2; Cov19Ind, 1). One Cov19Neg and one Cov19Aty case had mild symptoms without the need for oxygen supplementation and CT findings of the latter were only pre-existing bronchiectasis. One Cov19Neg died of severe pulmonary embolism without “pneumonia”. One case of Cov19Aty and one case of Cov19Ind (Fig. 2C and D) needed intubation for oxygen stabilization. However, CT images of these cases were difficult to interpret because of the superimposition of severe emphysema.

### 4. Discussion

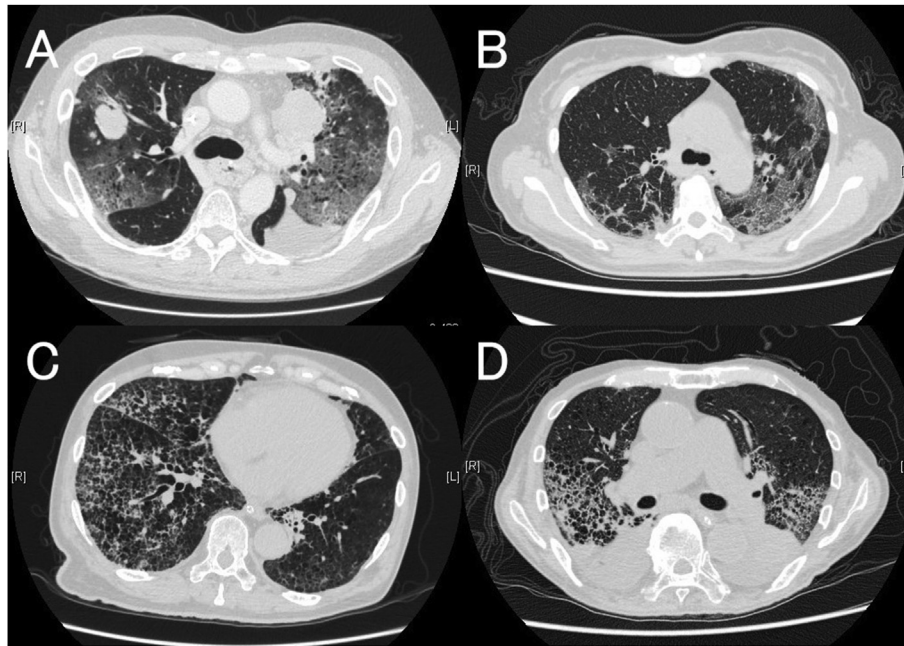
We examined the CT images, clinical characteristics, and laboratory data of COVID-19 and non-COVID-19 patients with suspected symptoms in an advanced care hospital in a relatively low prevalence region. We revealed that CT screening had a high sensitivity to COVID-19 for patients with suspected symptoms. When chest CT findings were typical for COVID-19, close contact, loss of taste or smell, low white blood cell count and high fibrinogen were good predictors for COVID-19.

We revealed most symptomatic COVID-19 cases showed typical CT findings. CT finding also had a high NPV. Thus, CT screening would be useful especially in ruling out COVID-19 for symptomatic patients in low prevalence regions. In addition, RSNA expert consensus statement [6] was a useful classification because of its simple criteria and because it achieved a high concordance rate among radiologists especially with typical images. Although articles suggested that the sensitivity of CT images varies, depending on the distribution of disease severity, the proportion of patients with comorbidities, and the proportion of asymptomatic patients [24], structured evaluation and reporting system of CT images such as RSNA expert consensus statement would provide higher diagnostic accuracy and inter-reader agreement [25]. On the other hand, attention should also be paid to the results that patients with typical CT images were not necessarily diagnosed with COVID-19. In our hospital, an advanced medical care institute in a relatively low COVID-19 prevalence

**Table 1 – Classification of CT images according to RSNA Expert Consensus Statement.**

| CT findings  | Cov19Neg | Cov19Aty | Cov19Ind | Cov19Typ | Total |
|--------------|----------|----------|----------|----------|-------|
| COVID-19     | 2        | 2        | 1        | 24       | 29    |
| non-COVID-19 | 19       | 49       | 79       | 21       | 168   |
| Total        | 21       | 51       | 80       | 45       | 197   |

Abbreviations: Cov19Neg: negative for pneumonia, Cov19Aty: atypical appearance, Cov19Ind: indeterminate appearance, Cov19Typ: typical appearance for COVID-19.



**Fig. 2** – Examples of non-COVID-19 with typical CT images (A, B) and COVID-19 cases with other than typical CT images (C, D). A: 55-year-old-male with nivolumab induced pneumonia arising during the treatment of esophageal cancer. CT images showed bilateral peripheral-dominant ground-glass opacities on pulmonary emphysema. Lung metastasis in the right upper lobe and preexisting left pleural effusion was also seen. B: 53-year-old-female with idiopathic pulmonary syndrome arising 6 months after an allogeneic hematopoietic stem cell transplant for acute myeloid leukemia. CT images showed bilateral-dominant peripheral ground-glass opacities. C: 68-year-old-male, current smoker, with chronic obstructive pulmonary disease. Two of three radiologists classified the CT images as Cov19Ind, the other Cov19Aty. D: 76-year-old-male, former smoker, with a history of recurrent aspiration pneumonia and chronic heart failure due to atrial fibrillation. All three radiologists classified the CT images as Cov19Ind. CT images of both cases were difficult to interpret because of the superimposition of severe emphysema. Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography.

region, the PPV of typical images was low, which was consistent with previous studies [24]. In fact, 5 of 21 Cov19Typ images in non-COVID-19 cases were related to the adverse events of cancer treatment (drug-induced interstitial

pneumonia, 4; radiation-induced interstitial pneumonia, 1), which might be seen especially in advanced care hospitals. Therefore, other information like clinical characteristics and laboratory data would also need to be considered for predicting COVID-19 in cases with Cov19Typ images.

In our study, several clinical characteristics and laboratory data were different between COVID-19 and non-COVID-19 patients with Cov19Typ images. Among these clinical characteristics, loss of taste or smell and close contact with COVID-19 patients were exclusive characteristics in our COVID-19 cases. Therefore, meticulous history taking was the most important. Alteration of smell or taste was one of the unique symptoms, probably due to elevated angiotensin-converting enzyme 2 (ACE2) expression in the olfactory neuroepithelium that induced SARS-CoV-2 entry as one of the mechanisms [26].

In laboratory data, we found the elevation of some markers of inflammation such as ferritin and fibrinogen, normal WBC count despite marked inflammation, and elevation of liver enzymes in COVID-19. C-reactive protein was elevated in both groups because Cov19Typ images could reflect intense inflammation irrespective of the cause. Coagulopathy as represented by pulmonary embolism and abnormal coagulation parameters such as elevation of D-dimer and fibrinogen was previously reported to be associated with COVID-19 [17,18]. Contrary to this evidence, D-dimer was elevated similarly in

**Table 2** – Causes of non-COVID-19 cases with Cov19Typ CT images.

| Causes  | No. of cases |
|---|--------------|
| <b>Interstitial pneumonia</b>                     | 11           |
| Acute exacerbation of IIPs                        | 1            |
| Collagen-Ips                                      | 3            |
| Drug-induced Ips                                  | 4            |
| Radiation-induced Ips                             | 1            |
| Post-transplant Ips                               | 2            |
| <b>Bacterial infection</b>                        | 4            |
| Community-acquired pneumonia                      | 3            |
| Aspiration pneumonia                              | 1            |
| <b>Alveolar hemorrhage</b>                        | 2            |
| <b>Pulmonary edema (congestive heart failure)</b> | 2            |
| Without bacterial infection                       | 1            |
| With bacterial infection (suspected)              | 1            |
| <b>Unknown causes</b>                             | 2            |
| Probably partial atelectasis                      | 1            |
| Probably bacterial infection                      | 1            |

Abbreviations: IIPs: idiopathic interstitial pneumonia, IPs: interstitial pneumonias.

**Table 3 – Clinical characteristics of patients with Cov19Typ CT images.**

|   | COVID-19 (N = 24) | non-COVID-19 (N = 21) | P-value |
|---|-------------------|-----------------------|---------|
| Age [years]                               | 63.5 (57.5–69.5)  | 74 (55–78)            | 0.11    |
| Sex (%)                                   |                   |                       | 0.34    |
| Male                                      | 18 (75%)          | 13 (62%)              |         |
| Female                                    | 6 (25%)           | 8 (38%)               |         |
| Smoking (%)                               |                   |                       | 0.22    |
| Current                                   | 13 (54%)          | 7 (33%)               |         |
| Former                                    | 5 (21%)           | 9 (42%)               |         |
| Never                                     | 3 (13%)           | 4 (19%)               |         |
| NA  | 3 (13%)           | 1 (5%)                |         |
| Symptom onset to CT [days]                | 6.5 (5–10)        | 5 (3–10)              | 0.29    |
| Close contact with COVID-19 patients (%)  | 7 (29%)           | 0 (0%)                | 0.01    |
| Comorbidity (%)                           |                   |                       |         |
| Any                                       | 16 (67%)          | 19 (90%)              | 0.08    |
| Respiratory disease                       | 4 (17%)           | 1 (5%)                | 0.20    |
| Cardiac disease                           | 3 (13%)           | 3 (14%)               | 0.86    |
| Hypertension                              | 8 (33%)           | 6 (29%)               | 0.73    |
| Diabetes                                  | 6 (25%)           | 4 (19%)               | 0.63    |
| Chronic renal failure                     | 1 (4%)            | 2 (10%)               | 0.47    |
| Active malignancy                         | 2 (8%)            | 11 (52%)              | <0.01   |
| Immune suppression                        | 3 (13%)           | 3 (14%)               | 0.86    |
| SpO <sub>2</sub> ≥ 94% on ambient air (%) | 9 (38%)           | 10 (48%)              | 0.49    |
| Loss of taste or smell (%)                | 5 (21%)           | 0 (0%)                | 0.05    |
| Endotracheal intubation (%)               | 8 (33%)           | 3 (14%)               | 0.14    |
| Alleviation of fever within 3 days (%)    | 9 (38%)           | 10 (48%)              | 0.49    |
| Laboratory data                           |                   |                       |         |
| White blood cells (/μL)                   | 5510 (4600–6675)  | 8300 (6500–11200)     | <0.01   |
| Neutrophils (/μL)                         | 4358 (3290–5469)  | 5331 (4784–10257)     | <0.01   |
| Lymphocytes (/μL)                         | 834 (649–1221)    | 956 (702–1378)        | 0.49    |
| Hemoglobin (g/dL)                         | 14.7 (13.6–15.9)  | 10.7 (9.7–12.7)       | <0.01   |
| Platelets (/μL)                           | 19.5 (15.5–23.3)  | 26.1 (13–35.7)        | 0.37    |
| C-reactive protein (mg/dL)                | 11 (3.4–13.5)     | 7.6 (2.7–15.4)        | 0.68    |
| Total protein (g/dL)                      | 6.6 (6.3–7.3)     | 6.1 (5.3–6.6)         | <0.01   |
| Albumin (g/dL)                            | 3.3 (2.9–3.9)     | 3.0 (2.8–3.2)         | 0.06    |
| Aspartate aminotransferase (U/L)          | 50 (43–83)        | 33 (22–47)            | <0.01   |
| Alanine aminotransferase (U/L)            | 49 (32–64)        | 21 (16–42)            | <0.01   |
| Lactate dehydrogenase (U/L)               | 417 (331–614)     | 320 (276–398)         | 0.05    |
| Amylase (U/L)                             | 59 (38–79)        | 70 (46–104)           | 0.38    |
| Creatinine (U/L)                          | 0.93 (0.74–1.06)  | 0.90 (0.68–1.30)      | 0.93    |
| Uric acid (mg/dL)                         | 5.6 (4.8–6.0)     | 6.3 (4.0–7.8)         | 0.49    |
| Creatine kinase (U/L)                     | 121 (52–299)      | 81 (44–111)           | 0.17    |
| Sodium ion (mEq/L)                        | 135 (133–138)     | 139 (137–140)         | 0.04    |
| Potassium ion (mEq/L)                     | 4.2 (3.8–4.5)     | 4.0 (3.9–4.3)         | 0.59    |
| Ferritin (ng/mL)                          | 693 (422–1223)    | 289 (197–471)         | 0.02    |
| PT–INR                                    | 1.01 (0.97–1.09)  | 1.02 (0.98–1.14)      | 0.38    |
| Fibrinogen (mg/dL)                        | 629 (518–700)     | 463 (374–610)         | <0.01   |
| D-dimer (μg/mL)                           | 1.1 (0.7–2.0)     | 2.4 (0.8–4.3)         | 0.12    |

Data are median (interquartile range) or n (%). P values were calculated by non-paired t-test, Mann–Whitney U test,  $\chi^2$  test, or Fisher's exact test, as appropriate.

both COVID-19 and non-COVID-19 in our study, probably because of the difference in the control group, where there were more patients with comorbid diseases especially active malignancies [27] in the present study than in other studies. On the other hand, fibrinogen was shown to be higher in COVID-19 patients, probably also as an acute phase reactant. Fibrinogen is known to be induced by interleukin-6, which plays an important role in cytokine storm in severe COVID-19 and could be a therapeutic target [28]. Therefore, fibrinogen could also be a clinically meaningful marker. WBC count was lower in COVID-19, but lymphocyte count, which was reported to be low in COVID-19, was similar in both groups in our study. This was probably because lymphopenia was not

necessarily seen in non-severe cases [23,29], and other causes of inflammation such as bacterial infection could show neutrophilia (relative lymphopenia).

In multivariate analysis, we clarified that WBC count and serum fibrinogen are good predictive markers for COVID-19 in patients with Cov19Typ images. Although there were some reports of the prediction model using clinical and radiological data, most predictions were evaluated for the patients without serious comorbidities visiting the emergency room in high prevalence areas [21]. This evidence could not be necessarily applied to a cohort in advanced care hospitals in relatively low prevalence areas, as in the present study, because clinical, imaging, and laboratory findings might be affected by

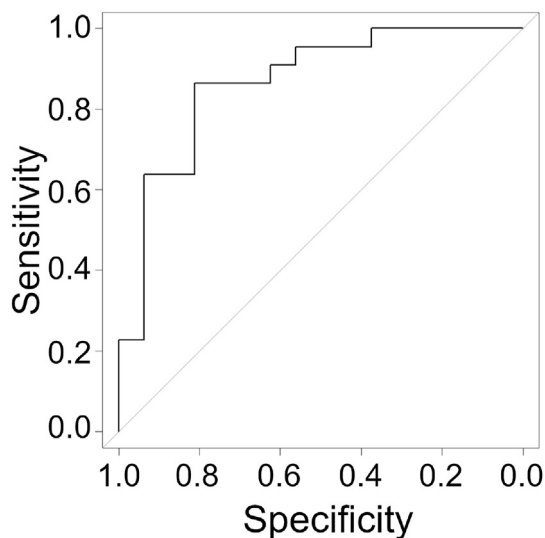
**Table 4 – Multivariate analysis for COVID-19 in cases with Cov19Typ CT images.**

|                              | Est. coefficients | S.E.   | z -value | P-value |
|------------------------------|-------------------|--------|----------|---------|
| (Intercept)                  | −0.5426           | 1.8924 | −0.287   | 0.77    |
| Fibrinogen (mg/dL)           | 0.0085            | 0.0033 | 2.602    | <0.01   |
| White blood cell count (/μL) | −0.0005           | 0.0002 | −2.752   | <0.01   |

Binomial logistic regression analysis (stepwise regression method) was performed for estimated COVID-19 in cases with Cov19Typ CT images. Variables included age, sex, lactate dehydrogenase, C-reactive protein, fibrinogen, D-dimer, aspartate aminotransferase, fibrinogen, and white blood cell count. Close contact and loss of taste or smell were omitted for multivariate analysis because no cases of non-COVID-19 had these characteristics. Ferritin was also omitted due to many missing data. The stepwise method finally selected fibrinogen and white blood cell count.

comorbid diseases. In fact, when our data was calculated using “Corona score”, one of the scoring systems predicting COVID-19 [30], 9 of 21 non-COVID-19 cases with Cov19Typ images were predicted as COVID-19, because only bilateral lung infiltrates with minimal inflammation could exceed lower cut-off value.

Attention should also be paid to patients with images other than Cov19Typ because it is difficult to assess the likelihood of COVID-19 in patients with mild or no symptoms who may show normal CT features [31], and in patients with respiratory comorbidities like emphysema and interstitial pneumonia



**Fig. 3 – The receiver operating characteristics (ROC) curve for COVID-19 in Cov19typ CT images. The predicted probability (P) of COVID-19 among cases with Cov19typ images was estimated according to the results of binomial logistic regression analysis:  $P = 1/(1+e^{-X})$ , where  $X = -0.5426 + 0.0085 * \text{fibrinogen (mg/dL)} - 0.0005 * \text{WBC (/}\mu\text{L)}$ . The area under the ROC curve was 0.866 (95% CI, 0.745–0.988). When a cut-off point for X was defined as a value  $\geq -0.0074$ , the sensitivity and the specificity were 0.863 and 0.813, respectively.**

which would obscure typical CT finding of COVID-19. Conversely, almost all symptomatic cases without background respiratory diseases presenting other than Cov19Typ images were non-COVID-19 in our study. Therefore, it seemed important to evaluate the probability of COVID-19 in symptomatic cases with Cov19Typ images.

This study has several limitations. First, this was a retrospective cohort study, and symptom reporting was voluntary. Thus, there were missing values. Second, the entry criteria could be biased because only the patients who were consulted to our dedicated team because of the symptoms or abnormal CT images suggestive of COVID-19 were included. Therefore, cases with atypical symptoms or images could be overlooked. Third, there was a small number of COVID-19 patients compared to non-COVID-19 patients because of the low prevalence. While the results cannot be applied in high prevalence areas, it is important to assess how to predict COVID-19 for the cases with comorbidities in relatively low prevalence regions like in our study.

## 5. Conclusion

We compared patients with COVID-19 and non-COVID-19 with symptoms in an advanced care hospital in a low prevalence region. Typical CT images have high sensitivity and high NPV but low PPV for patients with suspected symptoms in a low prevalence region. When chest CT finding is typical for COVID-19 pneumonia, close contact, loss of taste or smell, low WBC count and high fibrinogen data would be promising predictors of COVID-19.

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## Conflict of Interest

The authors declare that they have no conflicts of interest for this study.

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