Differential Diagnosis of COVID-19: Importance of Measuring Blood Lymphocytes, Serum Electrolytes, and Olfactory and Taste Functions

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Coronavirus disease 2019 (COVID-19) is associated with various symptoms and changes in hematological and biochemical variables. However, clinical features, which can differentiate COVID-19 from non-COVID-19, are not clear. We therefore examined the key clinical features of COVID-19 and non-COVID-19 patients. This study included 60 COVID-19 patients and 100 non-COVID-19 patients, diagnosed by PCR, and no significant differences in the age and sex were seen between the two groups. The frequencies of fatigue, loose stool, diarrhea, nasal obstruction, olfactory dysfunction, taste dysfunction, underlying hyperlipidemia, and the prescription of angiotensin II receptor blocker (ARB) were significantly higher in COVID-19 patients than those in non-COVID-19 patients. The counts of leucocytes, neutrophils, lymphocytes, eosinophils, monocytes, and basophils and the levels of chloride and calcium in blood of COVID-19 patients were significantly lower than those of non-COVID-19 patients. The frequencies of atypical lymphocytes and the levels of lactate dehydrogenase (LDH) and potassium were significantly higher in COVID-19 than those in non-COVID-19. The C-reactive protein (CRP) level in COVID-19 patients was significantly lower than that in non-COVID-19 patients, when we compared CRP levels among patients with elevated CRP. This study is the first to indicate that electrolyte levels and the frequency of atypical lymphocytes in COVID-19 are significantly different from those in non-COVID-19. Fatigue, loose stool, diarrhea, nasal obstruction, olfactory dysfunction, and taste dysfunction were the key symptoms of COVID-19. Furthermore, hyperlipidemia and ARB may be risk factors of COVID-19. In conclusion, leucocytes, leucocyte fractions, CRP, LDH, and electrolytes are useful indicators for COVID-19 diagnosis.

Keywords: angiotensin II receptor blocker; atypical lymphocyte; COVID-19; electrolytes; hyperlipidemia
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Introduction

The number of individuals with coronavirus disease 2019 (COVID-19) is currently increasing worldwide. The symptoms of this disease include fever, cough, fatigue, shortness of breath, myalgia, arthralgia, sore throat, and headache (Chen et al. 2020; Guan et al. 2020; Wang et al. 2020; Wu et al. 2020a; Zhang et al. 2020). Yan et al. (2020) examined the initial presentation of COVID-19 by analyzing patients with influenza-like symptoms and found that the frequencies of fever, ageusia, anosmia, headache, and myalgia/arthralgia were significantly higher in the COVID-

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19 patients than those in the non-COVID-19 patients, diagnosed using polymerase chain reaction (PCR). However, the prodrome of COVID-19 remains to be elucidated.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensinogen converting enzyme 2 (ACE2) to enter host cells (Hoffmann et al. 2020). ACE2 is widely distributed in vivo, such as in nasal cavity, oral cavity, lung, skin, heart, kidney, and intestine (Bourgonje et al. 2020). While ACE2 polymorphisms have been described in humans, genomic variants of SARS-CoV-2 have also been reported (Devaux et al. 2020; Forster et al. 2020; Shen et al. 2020). These suggest the diversity of COVID-19 symptoms.

In a multicenter European study (Lechien et al. 2020), olfactory and taste dysfunctions were reported in 85.6% and 88.8% of patients with COVID-19, respectively. Olfactory and taste dysfunctions were reported as prevalent symptoms of COVID-19 in Europe and North America (De Maria et al. 2020; Lechien et al. 2020; Yan et al. 2020). However, frequencies of olfactory and taste dysfunctions reported in China were less than 6% (Chen et al. 2020; Cui et al. 2020; Guan et al. 2020; Mao et al. 2020; Wang et al. 2020; Wu et al. 2020a). Ikehara et al. (2020) also showed none of 21 patients with COVID-19 complained of olfactory dysfunction in Japan. It is therefore not clear whether olfactory and taste dysfunction is important in many countries.

The clinical results of patients, such as the levels of C-reactive protein (CRP) in the blood, appear to be the important markers for assessing the severity of COVID-19 (Kermali et al. 2020). Laboratory findings from blood samples can also be used to differentiate COVID-19 from other diseases (Ferrari et al. 2020; Li et al. 2020c). Li et al. (2020c) compared the clinical results of patients positive and negative for COVID-19 by PCR analysis and found that the combination of eosinopenia with increased CRP level could be used to triage effectively suspected COVID-19 patients from other patients presenting fever. Ferrari et al. (2020) also compared the laboratory findings of these two groups of patients and found that blood tests could help in identifying for COVID-19. However, studies that comparatively analyze the clinical results from patient blood samples, such as the direct comparison between the clinical results of patients with positive and negative PCR analysis results, have been reported little. It also remains unclear whether laboratory findings on different clinical parameters can be used to identify and confirm COVID-19 on the first day of clinical examination.

Angiotensin (Ang) II acts on the adrenal cortex, and stimulates the release of the aldosterone. Aldosterone increases fluid and sodium retention by the kidney (Patel et al. 2017). ACE2 also play an important role to maintain fluid and electrolyte balance, because ACE2 changes Ang II to Ang-(1-7) (Cohen et al. 2020). Additionally, Dos-Santos et al. (2017) showed that intracerebroventricular injection of Ang-(1-7) increased water intake after osmotic stimulates. Furthermore, SARS-CoV-2 induces downregulation of ACE2 expression and shedding from the cell surface, resulting in an increase of Ang II and a decrease of Ang-(1-7) (Cohen et al. 2020). These suggest that serum electrolyte balance is affected by COVID-19, although the effect of Ang-(1-7) on serum electrolytes is unclear (Dos-Santos et al. 2017). Lippi et al. (2020) found that the levels of sodium, potassium, and calcium in severe COVID-19 patients were significantly higher than those in non-severe patients. However, the timing of blood collection was not clear. Additionally, to the best of our knowledge, a direct comparison between the serum levels of sodium, potassium, and calcium in COVID-19-positive and -negative patients has not yet been performed. It is therefore currently unclear whether electrolyte imbalance can be used as an indicator of COVID-19 on the first day of examination in patients.

Both false-positive and false-negative PCR results have been reported in the testing of COVID-19. Li et al. (2020a) reported a false-negative rate of approximately 20% in PCR. Tests with a sensitivity of 90% have also been assumed (West et al. 2020). Additionally, Fang et al. (2020) reported a low sensitivity for PCR. Furthermore, health care workers have potential exposures to COVID-19 by PCR. There is, therefore, an urgent need to identify symptoms and clinical results that can be used to help differentiate COVID-19 from other diseases with similar symptoms. In this study, we compared the symptoms and hematological and biochemical parameters of patients diagnosed as COVID-19 and non-COVID-19, judged by the PCR analysis.

Methods

Study design and participants

This study comprises a single-center retrospective analysis of patients with COVID-19 PCR analysis upon their first medical examination. COVID-19 PCR tests were performed in patients with COVID-19-like symptoms, such as fever, cough, fatigue, shortness of breath, myalgia, arthralgia, sore throat, olfactory dysfunction, taste dysfunction, and headache or those who have contacts with patients with COVID-19. All patients positive for COVID-19 by PCR analysis before May 15, 2020 (between February 14 and May 15, 2020) were included. One hundred patients negative for COVID-19 by PCR analysis were counted backwards to May 15, 2020 (between April 25 and May 15, 2020), and these 100 non-COVID-19 patients were included. The clinical data of these patients were collected from their medical records at the Nagoya City East Medical Center. This study was approved by the Research Ethics Committee of Nagoya City East Medical Center (20-04-310).

Symptoms

The prevalence of the recent symptoms, including fever, fatigue, cough, sore throat, shortness of breath, myalgia or arthralgia, headache, olfactory dysfunction, taste dysfunction, nasal discharge, nasal obstruction, sneeze, abnormal sensation in the throat, nausea or vomiting, loose stool, diarrhea, dizziness, sputum discharge, abdominal pain, otalgia, redness of the skin, frequent urination, edema of the arms, and legs, and chest pain upon the patients' first medical examination was examined.

Laboratory findings in blood

The levels of leucocytes, neutrophils, lymphocytes, eosinophils, monocytes, basophils, CRP, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, and calcium in the blood upon their first medical examination day were examined.

Underlying diseases and medication

The prevalence of hypertension, diabetes, coronary heart disease, hyperlipidemia, and asthma upon the patients' first medical examination were examined. We also examined the medication prescribed before the onset of COVID-like symptoms: angiotensin II receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACE inhibitor), calcium antagonist, diuretic, nonsteroidal anti-inflammatory drug (NSAID), inhaled steroid, and oral steroid.

Statistical analysis

Results are expressed as the mean ± standard error of the mean (SEM). A statistical comparison between the two groups was performed using the Chi-squared test for sex, symptoms, underlying diseases, medicines, blood types, and existence of laboratory data change and Mann-Whitney *U* test for age and levels of laboratory findings. $P < 0.05$ was used to indicate significant differences between results.

Results

Participant characteristics

Sixty patients (33 men and 27 women; age, 9-88 years; mean age, 51.4 ± 2.7 years) comprised the COVID-19 group, as judged by PCR-positive results. One hundred patients (54 males and 46 females; age, 16-95 years; mean age, 46.4 ± 2.1 years) comprised the non-COVID-19 group, as judged by PCR-negative results. The mean body temperatures of the COVID-19 (PCR-positive) and non-COVID-19 (PCR-negative) groups were 37.1°C ± 0.1 and 37.3°C ± 0.1, respectively. There were no significant differences in the age, sex, or body temperature between the positive and negative groups.

Prevalence of symptoms on the first medical examination day

As shown in Table 1, the frequencies of fatigue, loose stool, diarrhea, and nasal obstruction in COVID-19 patients were significantly higher than those in non-COVID-19 (PCR-negative) patients.

Table 1. The frequencies of symptoms on the first medical examination day.

Symptom	% (Number) PCR-positive	PCR-negative	P value
Fever	83.3% (50)	83.0% (83)	0.96
Fatigue	48.3% (29)	23.0% (23)	< 0.001
Cough	55.0% (33)	42.0% (42)	0.11
Sore throat	21.7% (13)	26.0% (26)	0.54
Shortness of breath	13.3% (8)	8.0% (8)	0.28
Myalgia or Arthralgia	13.3% (8)	12.0% (12)	0.81
Headache	21.7% (13)	19.0% (19)	0.68
Nasal discharge	8.3% (5)	16.0% (16)	0.16
Nasal obstruction	10.0% (6)	1.0% (1)	< 0.01
Sneeze	0.0% (0)	2.0% (2)	0.27
Abnormal sensation in the throat	8.3% (5)	2.0% (2)	0.13
Nausea or Vomiting	5.0% (3)	3.0% (3)	0.67
Loose stool	13.3% (8)	2.0% (2)	< 0.01
Diarrhea	38.3% (23)	15.0% (15)	< 0.001
Dizziness	5.0% (3)	2.0% (2)	0.29
Sputum	16.7% (10)	14.0% (14)	0.65
Abdominal pain	5.0% (3)	3.0% (3)	0.13
Otalgia	0.0% (0)	0.0% (0)	
Redness of the skin (Erythema)	1.7% (1)	2.0% (2)	0.88
Frequent urination	3.3% (2)	0.0% (0)	0.07
Edema of the arms and legs	1.7% (1)	0.0% (0)	0.20
Chest pain	1.7% (1)	6.0% (6)	0.19

Symptoms of 60 COVID-19 PCR-positive patients and 100 non-COVID-19 patients (PCR-negative) were examined.

Table 2. The frequencies of olfactory dysfunction and taste dysfunction.

Symptom	% (Number/Total patients) PCR-positive	PCR-negative	P value
Olfactory dysfunction	59.4% (19/32)	8.0% (8/100)	< 0.0001
Taste dysfunction	56.3% (18/32)	13.0% (13/100)	< 0.0001

Only 32 COVID-19 PCR-positive patients, who were inquired about olfactory and taste dysfunctions, were considered in the analysis, because we started inquiring the patients about olfactory and taste dysfunctions after April 5, 2020.

Table 3. The frequencies of the underlying diseases and medicines.

	% (Number) PCR-positive	PCR-negative	P value
The underlying diseases			
Hypertension	28.3% (17)	16.0% (16)	0.06
Diabetes	16.7% (10)	9.0% (9)	0.15
Coronary heart disease	13.3% (8)	7.0% (7)	0.18
Hyperlipidemia	21.7% (13)	8.0% (8)	< 0.05
Asthma	10.0% (6)	7.0% (7)	0.50
The type of medicine			
ARB	15.0% (9)	5.0% (5)	< 0.05
ACE inhibitor	1.7% (1)	1.0% (1)	0.71
Calcium antagonist	13.3% (8)	9.0% (9)	0.39
Diuretic	6.7% (4)	3.0% (3)	0.27
NSAID	8.3% (5)	5.0% (5)	0.40
Inhaled steroid	6.7% (4)	4.0% (4)	0.45
Oral steroid	1.7% (1)	3.0% (3)	0.60
Inhaled or oral steroid	8.3% (5)	7.0% (7)	0.76

The underlying diseases and medicines of 60 COVID-19 PCR-positive patients and 100 non-COVID-19 (PCR-negative) patients were examined.
ARB, angiotensin II receptor blocker; ACE inhibitor, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

Olfactory dysfunction and taste dysfunction were examined in 32 of 60 patients with COVID-19 (20 males and 12 females; age, 9-66 years; mean age, 40.8 ± 2.9 years) because we started inquiring the patients about olfactory and taste dysfunctions after April 5, 2020. The frequencies of olfactory dysfunction and taste dysfunction in 32 COVID-19 patients were significantly higher than those in 100 non-COVID-19 (PCR-negative) patients (Table 2). However, no patient complained of olfactory or taste dysfunction before we started inquiring about these, suggesting the importance of the interview about olfactory and taste dysfunction.

Associated underlying diseases and medication

We examined the underlying diseases and the medication prescribed. The frequency of hyperlipidemia was significantly higher in the COVID-19 group than in the non-COVID-19 (PCR-negative) group (Table 3). However, there were no significant differences between the two groups with respect to the frequencies of hypertension, diabetes, coronary heart disease, and asthma. The frequency of ARB prescription to treat clinical conditions, such as hypertension and heart failure, was also significantly higher in the COVID-19 group than in the non-COVID-19 (PCR-negative) group (Table 3).

Laboratory data on the first medical examination day

The data of leucocytes and leucocyte fractions in blood are shown in Table 4. The counts of leucocytes in the COVID-19 group was significantly lower than that in the non- COVID-19 (PCR-negative) group. The mean of leucocytes in non-COVID-19 (PCR-negative) group was higher than normal range, but the mean of leucocytes in the COVID-19 group was in the normal range. The percentage of patients with leucocyte counts above the normal range in the PCR-positive group was also significantly lower than that in the PCR-negative group. The percentage of patients with a leucocyte count below the normal range in the COVID-19 group was significantly higher than that in the PCR-negative group. Next, we examined differential count

Table 4. Laboratory finding of leucocytes on the first medical examination day.

Paragraph	PCR-positive	PCR-negative	P value
Leucocytes (normal range 3,500-8,000 per μL)			
Counts (cells/μL)	5,160 ± 196	8,285 ± 431	< 0.0001
Increased (No./total patients)	6.7% (4/60)	34.9% (29/83)	< 0.0001
Decreased (No./total patients)	8.3% (5/60)	1.2% (1/83)	< 0.05
Neutrophils (normal range 45.6-72.7%)			
% in leucocytes	75.7 ± 11.7	65.3 ± 1.5	0.54
Increased (No./total patients)	23.7% (14/59)	33.7% (28/83)	0.20
Decreased (No./total patients)	5.1% (3/59)	3.6% (3/83)	0.67
Counts (cells/μL)	3,780 ± 429	5,615 ± 379	< 0.0001
Lymphocytes (normal range 20.2-45.2%)			
% in leucocytes	24.5 ± 1.3	23.5 ± 1.2	0.54
Increased (No./total patients)	3.3% (2/59)	3.6% (3/83)	0.93
Decrease (No./total patients)	32.2% (19/59)	43.4% (36/83)	0.18
Counts (cells/μL)	1,236 ± 77	1,747 ± 86	< 0.0001
Finding of atypical lymphocytes			
% (No./total No. of patients)	16.9% (10/59)	3.0% (3/83)	< 0.01
Eosinophils (normal range 0.8-8.4%)			
% in leucocytes	0.95 ± 0.18	2.26 ± 0.51	< 0.001
Increased (No./total patients)	0.0% (0/59)	2.4% (2/83)	0.23
Decreased (No./total patients)	47.5% (28/59)	30.1% (25/83)	< 0.05
Counts (cells/μL)	49 ± 8	211 ± 86	< 0.0001
Monocytes (normal range 2.0-7.5%)			
% in leucocytes	9.6 ± 0.5	7.8 ± 0.3	< 0.01
Increased (No./total patients)	66.1% (39/59)	49.4% (41/83)	< 0.05
Decreased (No./total patients)	0.0% (0/59)	5.1% (3/83)	< 0.0001
Counts (cells/μL)	491 ± 30	636 ± 42	< 0.05
Basophils (normal range 0.3-1.9%)			
% in leucocytes	0.25 ± 0.04	0.43 ± 0.04	< 0.001
Increased (No./total patients)	0.0% (0/59)	1.2% (1/83)	0.40
Decreased (No./total patients)	62.7% (37/59)	32.5% (27/83)	< 0.001
Counts (cells/μL)	13.1 ± 2.4	29.3 ± 2.7	< 0.0001

Leucocytes of 60 COVID-19 PCR-positive patients and 83 COVID-19 PCR-negative patients were examined. Leucocyte fractions of 59 COVID-19 PCR-positive patients and 83 non-COVID-19 (PCR-negative) patients were also examined.

of leucocytes. The cell counts of neutrophils, lymphocytes, eosinophils, monocytes, and basophils in the COVID-19 group was significantly lower than that in the PCR-negative group. The percentages of basophils in leucocytes of COVID-19 group were significantly lower than those of the PCR-negative group. However, the percentages of monocytes in leucocytes of COVID-19 group were significantly higher than those of the PCR-negative group, and the number of COVID-19 patients with higher proportion of monocytes in leucocytes than the normal range was significantly more than that of non-COVID-19 patients. Additionally, the percentage of patients with atypical lymphocytes in the COVID-19 group was significantly higher than that in the PCR-negative group.

Laboratory data of CRP, GOT, GPT, BUN, creatinine, and LDH in blood are shown in Table 5. The CRP titer in the COVID-19 group did not differ significantly from that in the non-COVID-19 (PCR-negative) group. However, the CRP titer in the COVID-19 group was significantly lower than that in the PCR-negative group when we examined only patients with increased CRP levels. The titers of GOT and LDH in the COVID-19 group were significantly higher than those in the PCR-negative group.

Laboratory findings of serum electrolytes are shown in Table 6. The titer of potassium in the COVID-19 group was significantly higher than that in the negative group. Increased potassium levels were observed in only three COVID-19 patients. The percentage of patients with potas-

Table 5. Laboratory data of CRP, GOT, GPT, BUN, creatinine, and LDH on the first medical examination day.

Paragraph	PCR-positive	PCR-negative	P Value
C-reactive protein (CRP, normal range 0.0-0.3 mg/dL)			
Level (mg/dL)	2.8 ± 0.5	4.1 ± 0.7	0.99
Increased (No./total patients)	63.3% (38/60)	52.7% (49/83)	0.19
Level of only patients with increased CRP titer (mg/dL)	4.2 ± 0.7	7.0 ± 1.0	< 0.05
Glutamic oxaloacetic transaminase (GOT, normal range 13-33 U/L)			
Level (U/L)	32.4 ± 2.4	31.3 ± 3.7	< 0.01
Increased (No./total patients)	30.0% (18/60)	18.1% (15/83)	0.09
Glutamic pyruvic transaminase (GPT, normal range 6-27 U/L)			
Level (U/L)	29.4 ± 2.6	32.5 ± 3.4	0.56
Increased (No./total patients)	30.0% (18/60)	34.9% (29/83)	0.54
Blood urea nitrogen (BUN, normal range 8.0-22.0 mg/dL)			
Level (mg/dL)	14.7 ± 1.0	12.78 ± 0.6	0.14
Increased (No./total patients)	10.0% (6/60)	6.0% (5/83)	0.38
Creatinine (normal range 0.40-0.70 mg/dL)			
Level (mg/dL)	0.87 ± 0.04	0.85 ± 0.06	0.41
Increased (No./total patients)	30.0% (18/60)	16.9% (14/83)	0.06
Lactate dehydrogenase (LDH, normal range 119-229 U/L)			
Levels (U/L)	249 ± 13	203 ± 10	< 0.001
Increased (No./total patients)	25.0% (15/60)	18.1% (15/83)	0.32

Laboratory data of CRP, GOT, GPT, BUN, creatinine, and LDH of 60 COVID-19 PCR-positive patients and 83 COVID-19 PCR-negative patients were examined.

Table 6. Laboratory findings of electrolytes on the first medical examination day.

Paragraph	PCR-positive	PCR-negative	P value
Sodium (normal range 138-146 mEq/L)			
Level (mEq/L)	137.1 ± 0.7	138.0 ± 0.4	0.30
Increased (No./total patients)	0.0% (0/59)	0.0% (0/83)	
Decreased (No./total patients)	35.6% (21/59)	32.5% (27/83)	0.70
Potassium (normal range 3.6-4.9 mEq/L)			
Level (mEq/L)	4.10 ± 0.06	3.93 ± 0.04	< 0.05
Increased (No./total patients)	5.1% (3/59)	0.0% (0/83)	< 0.05
Decreased (No./total patients)	3.4% (2/59)	18.1% (15/83)	< 0.01
Chloride (normal range 99-109 mEq/L)			
Level (mEq/L)	101.3 ± 1.3	103.4 ± 0.4	< 0.05
Increased (No./total patients)	0.0% (0/59)	1.2% (1/83)	0.40
Decreased (No./total patients)	11.9% (7/59)	10.8% (9/83)	0.85
Calcium (normal range 8.7-10.3 mg/dL)			
Level (mg/dL)	8.82 ± 0.08	9.24 ± 0.07	< 0.0001
Increased (No./total patients)	0.0% (0/58)	1.2% (1/83)	0.40
Decreased (No./total patients)	32.2% (19/58)	6.0% (5/83)	< 0.0001

Levels of sodium, potassium, and chloride in 59 COVID-19 PCR-positive patients and 83 COVID-19 PCR-negative patients were examined. Levels of calcium in 58 COVID-19 PCR-positive patients and 83 COVID-19 PCR-negative patients were also examined.

Table 7. Laboratory finding and pneumonia on the first medical examination day.

Paragraph	Pneumonia-positive	Pneumonia-negative	P value
Neutrophils			
% in leucocytes	81.2 ± 14.9	56.3 ± 2.2	< 0.01
Level (cells/μL)	4,076 ± 540	2,736 ± 232	< 0.05
Lymphocytes			
% in leucocytes	23.0 ± 1.5	29.7 ± 2.2	< 0.05
(normal range 20.2-45.2%)			
Decrease (No./total patients)	37.0% (17/46)	7.7% (1/13)	< 0.05
Monocytes			
% in leucocytes	9.0 ± 0.5	11.8 ± 1.0	< 0.05
(normal range 2.0-7.5%)			
Increased (No./total patients)	37.0% (17/46)	84.6% (11/13)	< 0.01
C-reactive protein (CRP)			
Level (mg/dL)	3.4 ± 0.6	0.6 ± 0.3	< 0.001
(normal range 0.0-0.3 mg/dL)			
Increased (No./total patients)	69.6% (32/46)	21.4% (3/14)	< 0.01
Lactate dehydrogenase (LDH)			
Level (U/L)	266 ± 16	194 ± 15	< 0.01

Neutrophils, lymphocytes, and monocytes of 46 COVID-19 patients with pneumonias and 13 COVID-19 patients without pneumonias were examined. Levels of CRP and LDH in 46 COVID-19 patients with pneumonias and 14 COVID-19 patients without pneumonias were also examined.

sium levels below the normal range in the COVID-19 group was also significantly lower than that in the PCR-negative group. The titers of chloride and calcium in the COVID-19 group was significantly lower than that in the PCR-negative group. The percentage of patients with calcium levels below the normal range in the COVID-19 group was also significantly higher than that in the PCR-negative group.

The incubation periods

We examined the incubation period after contact with patients with COVID-19 since the exact incubation period was not clear. Among the 60 COVID-19 patients, 21 patients had an episode of contact with patients with COVID-19. In these patients, the incubation period was 5.1 ± 0.3 days (range, 2-8 days).

Prevalence of pneumonia

Forty-six (76.7%) of the 60 COVID-19 patients had pneumonia at the first medical examination. Thirty-four patients had pneumonia in both the lungs. Twelve patients had pneumonia in one lung. Nine patients had right-sided pneumonia, and two of them developed pneumonia in both the lungs during treatment. Three patients had left-sided pneumonia.

Relationship between pneumonia and laboratory findings

The association between the frequency of pneumonia and laboratory findings of COVID-19 patients at the first medical examination was examined (Table 7). The neutrophil count, CRP level, and LDH level in patients with pneumonia were significantly higher than those in patients without pneumonia. There were also significant differences of the percentage of neutrophils, lymphocytes, and monocytes in leucocytes between patients with and without pneumonia. Additionally, significant relationships were observed between the frequency of pneumonia and the frequencies of patients with decreased lymphocyte, increased monocytes, or increased CRP.

ABO blood group

We evaluated the frequency of ABO blood types among the subjects. The frequency of the AB blood type was significantly lower in the COVID-19 group than in the non-COVID-19 (PCR-negative) group (Table 8).

Progress after the first medical examination in patients with COVID-19

Fifty-six of 60 patients were hospitalized, and four patients were forced to stay at home. Five COVID-19 patients underwent endotracheal intubation. Two COVID-19 patients underwent tracheostomy. Three patients died. Three patients were transferred to different hospitals for extracorporeal membrane oxygenation therapy. Fifty patients were discharged after showing an improvement. The mean length of hospital stay was 16.9 ± 1.5 days (range, 4-61 days). Conditions were also cured in all

Table 8. The frequencies of blood types.

	% (Number/Total patients)		
Blood type	PCR-positive	PCR-negative	P value
A	50.0% (14/28)	33.3% (8/24)	0.23
B	14.3% (4/28)	25.0% (6/24)	0.33
AB	0.0% (0/28)	16.7% (4/24)	< 0.05
O	35.7% (10/28)	25.0% (6/24)	0.40

Blood type of 28 COVID-19 PCR-positive patients and 24 COVID-19 PCR-negative patients were examined.

Table 9. The frequency of pneumonia.

	% (Number/Total patients)		
	PCR-positive	PCR-negative	P value
Pneumonia	76.7% (46/60)	47.0% (47/100)	< 0.001

The frequencies of pneumonia in 60 COVID-19 PCR-positive patients and 100 COVID-19 PCR-negative patients were examined.

patients, who were forced to stay at home, and COVID-19 PCR-negative conversions were confirmed in these patients.

One patient had a recurrence of COVID-19, which was confirmed by PCR testing, 16 days after hospital discharge; this patient had twice tested negative on PCR tests performed before hospital discharge. Additionally, this patient had fever and was hospitalized again.

Diagnosis and progress of non-COVID-19 patients

Forty-seven of the 100 non-COVID-19 patients were diagnosed with pneumonia. Additionally, 52, 15, 15, 10, 2, and 2 of the 100 non-COVID-19 patients were diagnosed with upper respiratory inflammation, gastroenteritis, bronchitis, myositis/arthritis, urinary tract infection, and cervical lymphadenitis, respectively. There were patients who have two or three underlying diseases. Alcoholic hepatitis, appendicitis, congestive heart failure, or ovarian cancer was also observed in a certain patient. Importantly, the frequency of pneumonia was significantly lower in the non-COVID-19 group than in the COVID-19 group (Table 9, P < 0.001). None of the patients had undergone endotracheal intubation and tracheostomy. Apart from cancer, all other diseases/conditions had been cured in 99 patients. There have been no cases of patient death to date.

Discussion

In this study, the frequencies of fatigue, loose stool, diarrhea, nasal obstruction, olfactory dysfunction, and taste dysfunction in COVID-19 patients were significantly higher than those in the non-COVID-19 patients. However, Yan et al. (2020) showed no significant differences of fatigue, diarrhea, and nasal obstruction between COVID-19 PCR-positive and COVID-19 PCR-negative groups. Although the reasons for this discrepancy between our and their results are unclear, there are several possibilities. First, symptoms may differ between countries due to differences in climate, ethnic groups, and subtypes of SARS-CoV-2. Phylogenetic network analysis recently suggested that the subtypes of SARS-CoV-2 may differ between East Asia, Europe, and North America (Forster et al. 2020). Second, population was different. Yan et al. (2020) examined patients with influenza-like symptoms, although we examined patients with possibilities of COVID-19. They reported that 26% non-COVID-19 patients had fever, whereas 83% non-COVID-19 patients had fever in our study.

Recent studies reported that olfactory and taste dysfunctions were prevalent and important symptoms of COVID-19 in Europe and North America (De Maria et al. 2020; Lechien et al. 2020; Yan et al. 2020). However, low frequencies of olfactory and taste dysfunctions were reported in China and Japan (De Maria et al. 2020; Lechien et al. 2020; Yan et al. 2020; Ikehara et al. 2020). In our study, 59.4% of patients complained of olfactory dysfunction at the first medical examination day only after we started inquiring about this specific symptom, even though no patient complained of this symptom before we started inquiring about it. Lack of awareness of olfactory loss is common (Croy et al. 2014; Suzuki et al. 2018). Many patients do not notice olfactory dysfunction themselves. They often notice olfactory dysfunction only when pointed out by a family member or an acquaintance. Additionally, patients notice olfactory dysfunction only if they consciously try to smell an odor, and most patients who visit a hospital with other symptoms have not yet noticed any olfactory dysfunction. This may be a possible explanation for the observed differences in the prevalence of this symptom. Furthermore, olfactory test seems to help patients to notice olfactory dysfunction, and this may increase the percentage of complaint of olfactory dysfunction. Therefore, clinicians should inquire patients about the existence of olfactory dysfunction and perform olfactory tests, which are important in identifying olfactory dysfunction in patients with COVID-19.

Lipid rafts rich in cholesterol can harbor ACE2 receptors, which SARS-CoV-2 can bind to (Radenkovic et al. 2020). High cholesterol levels are associated with a higher concentration of lipid rafts and an increase in the binding of SARS-CoV-2 (Radenkovic et al. 2020). To the best of our knowledge, the direct comparison of the hyperlipidemia status between patients who tested positive and negative for COVID-19 in PCR tests has not been reported. This study showed that the percentage of COVID-19 patients with hyperlipidemia was significantly higher than that of non-COVID-19 patients with hyperlipidemia, which suggests that hyperlipidemia serves as a risk factor for COVID-19.

The present study showed that the frequency of ARB prescription was significantly higher in the COVID-19 group than in the non-COVID-19 group. Although the underlying mechanism cannot be elucidated easily, the effect of ARBs on ACE2 may play a role. ARBs have been reported to enhance ACE2 expression in rats (Ferrario et al. 2005; Jessup et al. 2006). Although based on guidelines provided by the WHO, changes in antihypertensive therapy under the current COVID-19 pandemic are not recommended before compelling evidence is published in favor of such changes, the findings of the current study suggest that ARBs may increase the risk of COVID-19 in humans.

In the present study, the cell counts of leucocytes, neutrophils, lymphocytes, eosinophils, monocytes, and basophils were found to be significantly decreased in COVID-19 patients, which is consistent with the results reported by Li et al. (2020c) and Ferrari et al. (2020). This study also showed that the levels of LDH in the blood were significantly increased in COVID-19 patients, which is consistent with the findings of Ferrari's study (2020). Taken together, these findings suggest that an increase in the LDH levels accompanied by a decrease in the levels of leucocytes, neutrophils, lymphocytes, eosinophils, monocytes and basophils in the blood is indicative of COVID-19. However, the percentages of monocytes in leucocytes of COVID-19 group were significantly higher than those of the non-COVID-19 group, and the number of COVID-19 patients with higher proportion of monocytes in leucocytes than the normal range was significantly more than that of non-COVID-19 patients. This suggests that COVID-19 reduces monocytes counts, but increase the proportion of monocytes in leucocytes, although Li and Ferrari did not examine the percentage of leucocyte fractions. The average level of leucocytes in COVID-19 patients was also in the normal range in our study, whereas that in non-COVID-19 was more than the normal range. The percentage of patients with leucocytes above the normal range in the COVID-19-positive group was significantly lower than that in the negative group. These suggest that leucocyte counts, which are not more than the normal range, suspect COVID-19.

Weinberg et al. (2020) and Gérard et al. (2020) observed atypical lymphocytes in patients with COVID-19. However, atypical lymphocytes have also been observed in patients with other infections. We therefore compared this marker between the COVID-19 and non-COVID-19 groups. We found that the percentage of atypical lymphocytes in the blood of COVID-19 patients was higher than that in the blood of non-COVID-19 patients.

Ferrari et al. (2020) found that the CRP titer in the COVID-19 group was significantly higher than that in the non-COVID-19 group. Similarly, Li et al. (2020c) found that the univariate model odds ratio (95% confidence interval) of a CRP increase was 7.89 and that the combination of eosinopenia with an elevated CRP could be used to effectively triage suspected COVID-19 patients from other patients. However, there were no significant differences in the titer of CRP and the percentage of patients with increased CRP between COVID-19 and non-COVID-19 patients in our study, although 63.3% COVID-19 patients had an elevated CRP. Additionally, the CRP titer in the COVID-19 patients with increased CRP level was significantly lower than that in the non-COVID-19 patients with increased CRP. This suggests that COVID-19 increases the levels of CRP, while the degree of the CRP increase in COVID-19 patients is weaker than that in patients with other infectious diseases.

In the present study, the percentage of patients with serum calcium levels below the normal range was significantly higher in the COVID-19 group than in the non-COVID-19 group. Moreover, the level of calcium in COVID-19 patients was significantly lower than that in the non-COVID-19 patients. This is consistent with the study of Lippi et al. (2020), who reported that the level of calcium in the blood of severe COVID-19 patients was significantly lower than that in patients with less severe COVID-19. Lippi et al. (2020) also showed that the sodium levels in the blood of severe COVID-19 patients were significantly lower than in non-severe COVID-19 patients. Additionally, our study showed that the serum sodium levels decreased by over 30% in COVID-19 patients. Although it is not easy to elucidate the underlying mechanism, hyponatremia may be associated with increase of fluid retention by Ang II, because COVID-19 downregulates ACE2 which converts Ang II to Ang-(1-7) (Cohen et al. 2020). However, there were no significant differences of blood sodium levels between the COVID-19 and non-COVID-19 groups in the present study. Hence, this suggests that both COVID-19 and other infectious diseases could decrease the levels of sodium in blood, albeit Lippi et al. (2020) did not examine the differences between COVID-19 and non-COVID-19 cases. Lippi et al. (2020) also showed no significant differences of chloride in blood between severe and non-severe COVID-19, whereas we showed significant differences of chloride between COVID-19 and non-COVID-19. In the present study, the percentage of COVID-19 patients with decreased potassium levels was significantly lower than in non-COVID-19 patients. However, potassium levels above the normal range were observed in only three COVID-19 patients, but not in non-COVID-19 patients. Additionally, Kang et al. (1992) reported that the serum potassium levels decreased in patients with influenza, although it is important to distinguish influenza from COVID-19. Taking these results into account, the decrease in the potassium levels in the blood of patients with COVID-19 may be smaller than that in patients with other infections, such that an increase in the potassium levels above the normal range may be indicative of COVID-19. Furthermore, our results suggest that the monitoring of electrolytes could help to confirm suspected cases of COVID-19.

Recently, Mumm et al. (2020) showed that 7 male patients out of 57 patients with COVID-19 had urinary frequency, suggesting that it could be an important symptom in the diagnosis of COVID-19 in male. In the present study, two females complained of frequent urination, suggesting that COVID-19 causes frequent urination not only in male but also in female patients.

The association between sneezes and COVID-19 has been inadequately reported. Sneezes are caused by various diseases such as allergic rhinitis, and it is unclear whether sneeze is common symptom or not. In the present study, no patients complained of sneezes as the recent symptoms. Considering this, we suggest that sneezes may be not common in COVID-19.

The CRP level is associated with disease severity and mortality in patients with COVID-19 (Kermali et al. 2020). However, it is unclear whether the laboratory findings, such as CRP, are associated with the existence of pneumonia in patients with COVID-19. This study showed that neutrophil, lymphocytes, monocytes, CRP, and LDH are markers suggesting the existence of pneumonia in patients with COVID-19.

Ang I is converted by the angiotensin-converting enzyme-1 (ACE1) to Ang II. The ACE1 polymorphism was shown to be correlated with the prevalence of COVID-19 (Delanghe et al. 2020). It was also reported that the variation in ACE1 was modulated by the ABO-blood group locus (Gassó et al. 2014). Additionally, one human gene variant that may explain differences of individual response to COVID-19 lies in the region of the genome that determines ABO blood type (Callaway et al. 2020). These results suggest that COVID-19 may be associated with ABO blood type. It has been reported that patients with A blood type have a higher risk of SARS-CoV-2 infection in China (Fan et al. 2020; Li et al. 2020b; Wu et al. 2020b). The frequency of the A blood type was higher in the COVID-19 group than in the non-COVID-19 group in our study, but the difference was not significant. On the other hand, in USA, Latz et al. (2020) reported that A blood type had no correlation with COVID-19, and B and AB blood types were associated with higher odds of positive for the disease. The frequency of the AB blood type was also significantly lower in the COVID-19 group than in the non-COVID-19 group in the present study. While it is not easy to explain this discrepancy, the association between ABO blood type and COVID-19 may differ between countries due to differences in the subtypes of SARS-CoV-2, the polymorphism of ACE1, ethnic groups, and so on. Although, to our knowledge, no study examined the association between ABO blood type and COVID-19 in Japan, this study suggests that people with AB blood type may have a decreased risk for infection with SARS-CoV-2 in Japan.

In conclusion, we demonstrate that the symptoms and clinical results of suspected COVID-19 cases upon their first medical examination can provide a basis for the initial identification and subsequent confirmation of COVID-19. However, it is worth noting that the present study was limited by its small sample size. Therefore, further studies with larger sample sizes will be needed to confirm and develop this result.

Conflict of Interest

The authors declare no conflict of interest.

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