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A study on SARS-CoV-2 infected patients with measured serum zinc levels during home care

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Abstract

Background: COVID-19 is an infectious disease caused by the SARS-CoV-2 virus and causing pandemics around the world. Zinc is an essential trace element and important for maintaining immune function. Serum zinc level has been reported to be low in severe cases of COVID-19.

Patients and methods: Patients who were diagnosed with SARS-CoV-2 infection were requested to be examined by our hospital while waiting at home were included. Medical history was heard, body temperature and blood oxygen saturation was measured, blood was collected, and lung CT examination was performed.

Results: The mean age of 102 patients was 39.7 y/o. There were no cases of fever with a body temperature of 37.5 ℃ or higher. Mean serum zinc level was 79.1μg/dL. Comparing serum zinc levels with healthy individuals by age, the serum zinc levels were significantly lower in COVID-19 cases over 50 y/o. Pneumonia findings was found in 54 cases (52.9%). Patients with pneumonia were significantly older than those without pneumonia (48.3 vs 30.1 y/o). Serum zinc levels were significantly lower in patients with pneumonia than in patients without pneumonia (75.5 vs 83.2 μg/dL). Dysosmia and dysgeusia were seen in 36 cases (35.3%). There were significantly younger ages compared to those without dysosmia and dysgeusia (34.4 vs 42.6 y/o). There was no difference in serum zinc levels depending on the presence of dysosmia or dysgeusia.

Conclusion: Serum zinc levels were involved in the development of SARS-CoV-2 infection and pneumonia. The onset of dysosmia or dysgeusia was not associated with serum zinc levels.

Key words: SARS-CoV-2, COVID-19, Zinc, Pneumonia, Dysosmia, Dysgeusia

Statements about COI: The authors declare no conflict of interest associated with this manuscript.

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Introduction

COVID-19 is a viral infection caused by SARS-CoV-2 virus that occurs in Wuhan, China and causes pandemics all over the world [1]. In Japan, as of November 2021, 1.7 million people were infected and 18000 people died. Vaccination is progressing and therapeutic drugs are being developed, but the current situation is that they have not yet converged.

Zinc is one of the essential trace elements and plays various important roles in the living body, especially for maintaining immune function and reported to have effect of blocking the

invasion and proliferation of pathogenic viruses [2,3]. It has been also pointed out that it may be effective in SARS-CoV-2 infection [4]. There are some reports investigating COVID-19 cases and serum zinc levels, in which zinc levels were low in severe cases and fatal cases, suggesting a link between COVID-19 and zinc [5,6,7,8,9,10].

One of the characteristics of COVID-19 is that dysosmia and dysgeunia often occur. However, there is only one report on zinc levels and dysosmia, and it is reported that it is not related to zinc concentration [11].

We had cases of SARS-CoV-2 infection who were on stay at home and were asked to undergo a test to determine the need for hospitalization. We have investigated the relationship between these patients and serum zinc levels.

Patients and methods

SARS-CoV-2 infectious disease is classified as type 2 infectious diseases in Japan, and infectious diseases in those categories require isolation. However, due to the increase in the number of infected cases, there was a situation where we had to wait at the hotel due to the shortage of hospital beds, and the number of cases waiting at home also increased. The Medical Coordination Headquarters, which coordinates the hospitalization of COVID-19 patients in Miyagi Prefecture, has asked medical institutions to inspect the cases that were judged to require severity determination among the cases waiting at home. The subjects of this study were cases diagnosed with SARS-CoV-2 infection between October 2020 and February 2021, and requested to assess the severity while waiting at home. Patients were planned to visit to our hospital from 10 am to 12 am. After arrival we asked the medical history, measured oxygen saturation and body temperature, collected blood, and performed lung CT examination. CT was read by a radiologist, and the case with the shadow characteristic of corona pneumonia was judged to have pneumonia. At the time of hearing the medical history, we also asked about the presence or absence of taste and smell abnormalities. Data from our staff (385 cases) were used to compare serum zinc levels as healthy individuals.

For statistical processing, Student's t-test and χ-square test were performed, and $p < 0.05$ was considered to be significantly different.

This paper has been approved by the Ethics Committee of the Sendai City Medical Center (2021-0052).

Results

A total of 102 patients were included in the study with a mean age of 39.7 ± 16.2 y/o (**Table 1**). The gender was 55 males and 47 females. Of these, 92 were symptomatic and 10 were asymptomatic. There were no cases in which the body temperature measured on the day of the examination was 37.5℃ or higher. Oxygen saturation was 96% or higher (mild) in 95 cases (93.1%), 94-95% (moderate I) in 1 case (1.0%), and 93% (moderate II) in 1 case (1.0%) and 5 unknown cases (4.9%). In symptomatic cases, the average time from onset to examination was 9.9 ± 4.7 days. At blood sampling, CRP, which reflects the degree of inflammation, was 0.68 ± 1.68 mg/dL, with a median of 0.15 mg/dL. The serum zinc level was 79.1 ± 12.7 μg/dL (reference value 80-130 μg/dL), which was the lower limit of the reference value. The relationship between serum zinc levels and age showed

Table 1. | Characteristics of SARS-CoV-2 infected patients

No of cases	102 cases
Age	39.7±16.2（34.5） y/o
M/F	M：55　F：47 cases
Symptom	yes：92　no：10 cases
Fever（＞37.5℃）	0 case
O_2 saturation ≥96%	95 cases（93.1%）
94-95%	1 case（1.0%）
93%	1 case（1.0%）
unclear	5 cases（4.9%）
Days from onset	9.9±4.7（10） days
CRP	0.68±1.68（0.15） mg/dL
Zn	79.1±12.7（80） μg/dL

mean±SD（median）

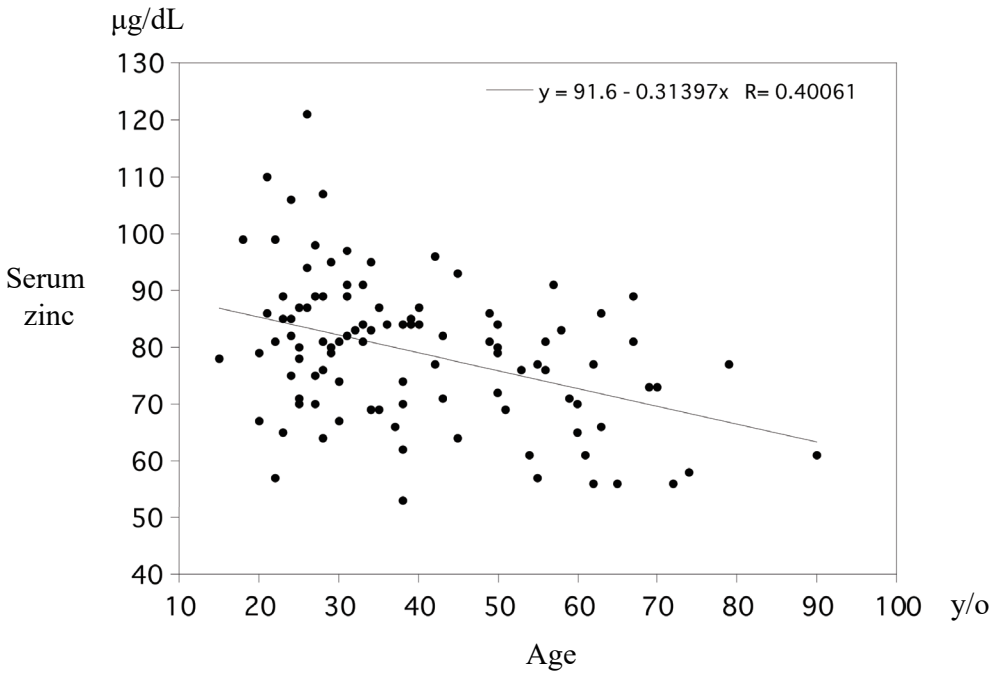

Fig. 1. | Relationship between serum zinc level and age in SARS-CoV-2 infected patients

Table 2. | Comparison of serum zinc levels between healthy control and SARS-CoV-2 infected patients by age

	Age	20s	30s	40s	50s	≥60	Total
Control	Serum zinc (μg/dL)	82.6 ± 11.2	82.5 ± 11.8	81.9 ± 11.7	86.4 ± 12.4	81.6 ± 13.0	82.9 ± 11.7
	n	147	114	58	53	13	385
SARS-CoV-2	Serum zinc (μg/dL)	84.3 ± 13.9	79.0 ± 10.8	82.1 ± 9.6	75.5 ± 19.0	69.1 ± 10.9	79.1 ± 12.7
	n	36	26	10	14	16	102
	p value	0.50	0.16	0.94	<0.001	0.01	0.007

mean ± SD

negative correlation (**Fig.1**). Comparing the serum zinc levels investigated by our hospital by age, there was no difference from the staff (healthy subjects) up to the age of 40s, but the serum zinc levels were significantly lower in the positive cases in the age group of 50s and over 60 y/o (**Table 2**). Regarding the relationship between serum zinc levels and CRP, zinc levels tended to be low in cases with high CRP, and all three cases with 4.0 mg /dL or higher were below the reference value (**Fig.2**).

In these patients, the number of cases showing pneumonia on CT was 54 (52.9%), which was more than half (**Table 3**). The relationship between pneumonia findings and age was 48.3 ± 16.0 y/o for those with pneumonia findings and 30.1 ± 9.7 y/o for those without pneumonia findings, which were significantly more common in the elderly (**Fig.3**). The frequency of pneumonia by age group showed a large difference: 7/36 (19.4%) in the 10-20 age group, 13/26 (50.0%) in the 30s group, 7/10 (70.0%) in the 40s group, 11/14 (78.6%) in the 50s group, and 16/16 (100.0%) in the over 60 y/o group. In terms of gender, 33 males (60.0%) and 21 females (44.7%) presented with pneumonia. Of the 10 asymptomatic cases, 8 had pneumonia findings. CT findings of a typical case without symptom was shown in **Fig.4**. The oxygen saturation was slightly lower in patients with pneumonia: 96% or more (mild disease) in 50 patients, 94-95% (moderate I) in 1 patient, and 93% (moderate II) in 1 patient, and 96% or more in all patients without pneumonia. There was no difference in the number of days elapsed from the onset depending on the presence or absence of pneumonia findings. CRP was 1.15 ± 2.18 mg/dL with pneumonia and 0.14 ± 0.44 mg/dL without pneumonia, showing a significant difference (p =0.002). Serum zinc levels were 75.5 ± 11.0 μg/dL with pneumonia findings and 83.2 ± 13.3 μg/dL without pneumonia findings, which were significantly lower in patients with pneumonia (p=0.002) (**Fig.5**). Even in cases

of younger than 40 y/o with low frequency of pneumonia findings, serum zinc levels were 77.4 ± 10.5 μg/dL with pneumonia (n = 20) and 84.3 ± 13.4 μg/dL without pneumonia (n = 42), which were significantly lower in patients with pneumonia (p = 0.03). In cases with a serum zinc level of 80 μg / dL or higher, 22 of 53 cases (41.5%) had pneumonia findings, but in cases of less than 80 μg / dL, 32 of 49 cases (65.3%) had pneumonia findings, which was significantly higher (p = 0.016).

There were 36 cases with dysosmia or dysgeusia in 35.3% of cases (**Table 4**). It was found in 18 of 55 males in 32.7% and in 18 of 47 females in 38.3%. The age was 34.4 ± 13.2 y/o with dysosmia or dysgeusia and 42.6 ± 17.0 y/o without dysosmia nor dysgeusia, which was significantly more common among young people (p = 0.008) (**Fig.6**). There was no difference in time from onset. CRP was 0.32 ± 0.96 mg/dL with dysosmia or dysgeusia and 0.87 ±1.95 mg/dL without dysosmia nor dysgeusia, which tended to be higher in cases without dysosmia nor dysgeusia (p = 0.06). The serum zinc level was 80.2 ± 14.8 μg/dL with dysosmia or dysgeusia, and 78.6 ± 11.4 μg/dL without dysosmia nor dysgeusia (**Fig.7**). The findings of pneumonia were 10/36 (27.8%) with dysosmia or dysgeusia and 44/66 (66.7%) without dysosmia nor dysgeusia, which was less common with dysosmia nor dysgeusia (p <0.001).

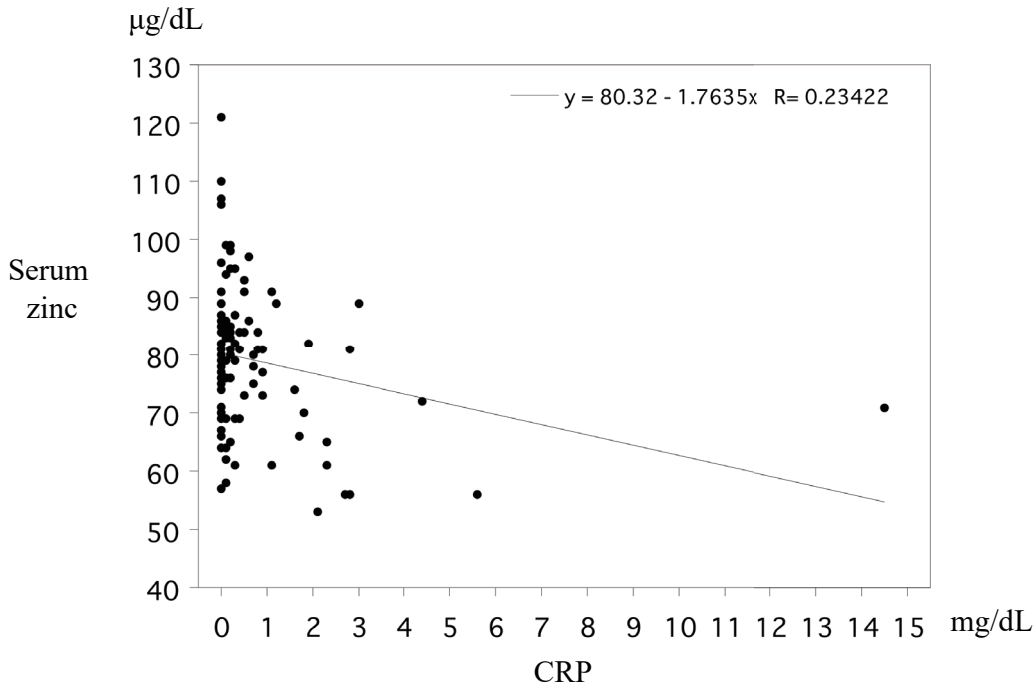

Fig. 2. | Relationship between serum zinc level and CRP in SARS-CoV-2 infected patients

Table 3. | Comparison between with and without pneumonia on CT examination

	Pneumonia (+)	Pneumonia (-)	p value
No of cases(%)	54 cases (52.9%)	48 cases (47.1%)	
Age	48.3 ± 16.0 (49.5) y/o	30.1 ± 9.7 (27.5) y/o	p<0.001
M/F	M:33 F:21 cases	M:22 F:26 cases	p=0.07
Symptom	yes：46 no：8 cases	yes：46 no：2 cases	p=0.12
O_2 saturation ≥96%	50 cases	45 cases	p=0.41
94-95%	1 case	0 case	
93%	1 case	0 case	
unclear	2 cases	3 cases	
Days from onset	9.2 ± 4.7 (9) days	10.5 ± 4.6 (10) days	p=0.21
CRP	1.15 ± 2.18 (0.5) mg/dL	0.14 ± 0.44 (0) mg/dL	p=0.002
Zn	75.5 ± 11.0 (76.5) μg/dL	83.2 ± 13.3 (83.5) μg/dL	p=0.002

mean ± SD（median）

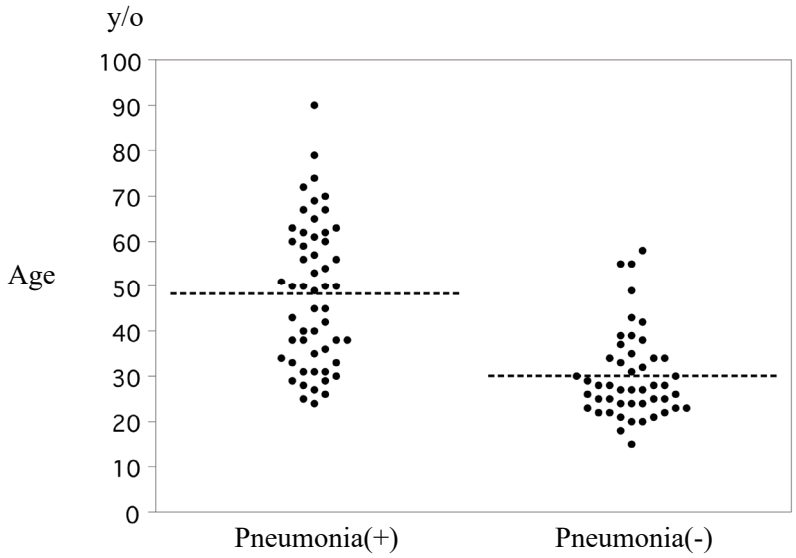

Fig. 3. Age of patients with or without pneumonia findings on CT examination

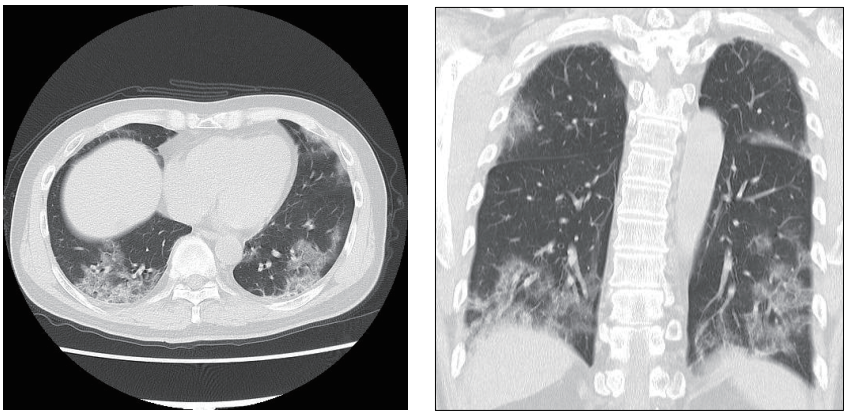

Fig. 4. CT findings of a COVID-19 patient without symptom.
60 y/o. Male. A close contact with COVID-19 patient and diagnosed as SARS-CoV-2 infection by PCR examination 6 days before a visit to our hospital. He is a smoker and under treatment for high blood pressure and diabetes mellitus. Body temperature 36.2°C, oxygen saturation 97%. He had no symptom of COVID-19. Serum Zinc 65μg/dL, CRP 2.3 mg /dL, D-dimer 1.43 μg/mL, white blood cell (WBC) count 5580/mm^3, lymphocyte count 1230 /mm^3. CT showed ground-glass opacity (GGO) in bilateral lungs.

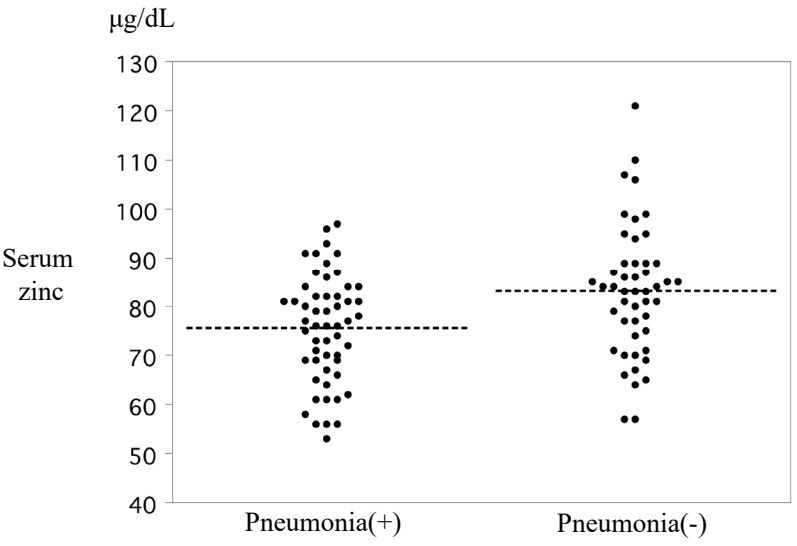

Fig. 5. Serum zinc levels of patients with or without pneumonia findings on CT examination

Table 4. | Comparison between with and without dysosmia/dysgeusia

	Dysosmia/Dysgeusia (+)	Dysosmia/Dysgeusia (-)	p value
No of cases (%)	36 cases (35.3%)	66 cases (64.7%)	
Age	34.4 ± 13.2 (28.5) y/o	42.6 ± 17.0 (39) y/o	p=0.008
M/F	M:18 F:18 cases	M:37 F:29 cases	p=0.56
Days from onset	10.1 ± 5.0 (10) days	9.7 ± 4.5 (10) days	p=0.66
CRP	0.32 ± 0.96 (0) mg/dL	0.87 ± 1.95 (0.25) mg/dL	p=0.06
Zn	80.2 ± 14.8 (80) μg/dL	78.6 ± 11.4 (80.5) μg/dL	p=0.56
Pneumonia (+)	10 cases (27.8%)	44 cases (66.7%)	p<0.001

mean ± SD (median)

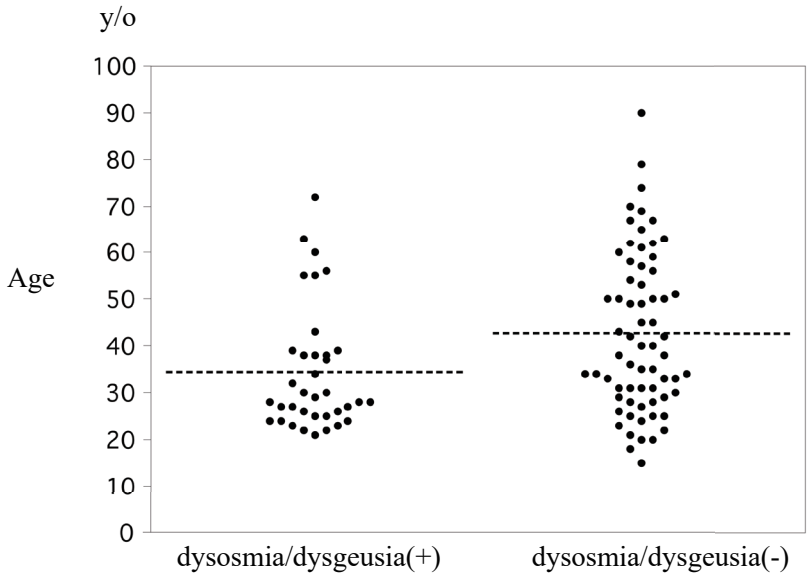

Fig. 6. | Age of patients with or without dysosmia/dysgeusia

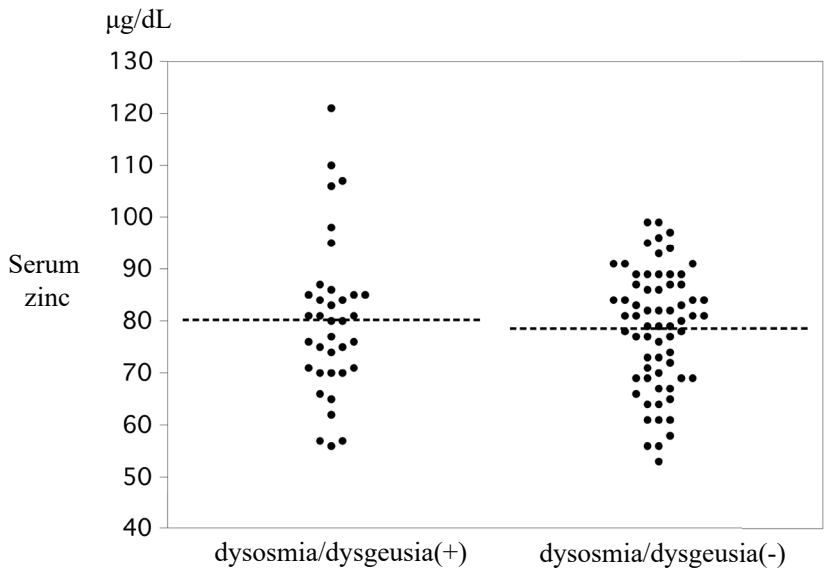

Fig. 7. | Serum zinc levels of patients with or without pneumonia findings on CT examination

Discussion

The 102 cases examined this time are cases in which SARS-CoV-2 infection was confirmed by PCR and were not treated such as oxygen inhalation during home medical treatment due to lack of hospital beds. There were no cases of fever with a body temperature of 37.5℃ or higher at the time of consultation. Oxygen saturation was also normal in 95 of the 97 measured cases (mild), not including severe cases. The average CRP, which indicates the degree of inflammation, was 0.68 ± 1.68 mg / dL, and the median was 0.15 mg / dL, and most of them were mildly ill patients. Lung CT examinations were also performed on these cases, and 52.9%, more than half, pointed out the findings of ground-glass opacity characteristic of COVID-19. Pneumonia was seen in 8 of the 10 asymptomatic patients. In a study of 104 passengers on the cruise ship Diamond Princess, where SARS-CoV-2 cluster infection occurred, 22 of 28 (79%) symptomatic cases had pneumonia, and 41 of 76 (54%) asymptomatic cases also had pneumonia on CT, and there was a discrepancy with clinical symptoms [12]. Therefore, it is considered that searching for the presence or absence of pneumonia by CT examination is useful for preventing respiratory failure and not missing the timing of starting treatment. When the cases with pneumonia images were examined by age in our case, pneumonia was observed in 19.4% of the cases under 30 y/o, but pneumonia findings were observed in all cases over 60 y/o. Careful follow-up is required because it has been reported that elderly people are more likely to become ill.

Zinc is one of the essential trace elements contained in the body in about 2 g, and plays an important role in maintaining the intracellular function [13]. At the time of deficiency, various deficiency symptoms such as decreased immunity, susceptibility to infection, prolonged wound healing, and dysgeusia appear [14,15]. A survey of serum zinc levels of residents conducted in Japan has pointed out a decrease in serum zinc levels, especially in the elderly [16]. Recently, in viral respiratory infections, a study of 25 RCTs reported that zinc administration was effective in reducing severity and shortening the duration [17]. Razzaque et al. reported zinc has the effect of suppressing intracellular invasion and intracellular proliferation in SARS-CoV-2 infection, so zinc deficiency may increase the risk of aggravation in SARS-CoV-2 infection and administration of zinc may have a therapeutic effect [3]. However, there are few reports on the association between COVID-19 and zinc in clinical cases, and the association with dysgeusia is unclear.

The serum zinc level of the COVID-19 patients examined this time was 79.1 ± 12.7 μg/dL, which was about the same as the lower limit of the reference value (80-130 μg/dL). We have already reported zinc levels in 52 outpatients or inpatients, most of whom were mildly ill as in these cases, but the values were as low as 66.8 ± 12.1 μg/dL [10]. This may be due to the difference in the time of blood collection: in the previous report, blood was collected between 15:00 and 16:00, but in this study, blood was collected between 10:00 and 12:00, and the value was lower in the afternoon than in the morning due to diurnal variation [18]. An association was found between lower serum zinc and SARS-CoV-2 infection with increasing age. Comparing the blood sampling data of our hospital staff collected in the morning as the data of healthy subjects (n = 385, 82.9 ± 11.7 μg/dL), the value was significantly lower in the COVID-19 patients (79.1 ± 12.7 μg/dL). When compared by age group, there was no difference in serum zinc level between the COVID-19 patients and healthy subjects under 50 y/o, but serum zinc level of the COVID-19 patients was statistically lower compared to healthy subjects at 50 y/o or over. A comparison of zinc levels with and without pneumonia was significantly lower in patients with pneumonia (75.5 ± 11.0 vs. 83.2 ± 13.3 μg/dL). These results suggest a relationship between SARS-CoV2 infection, the presence or absence of pneumonia, and serum zinc levels.

Several reports of serum zinc levels in COVID-19 patients have been made in relation to aggravation and mortality. Yasui et al. measured serum zinc levels in 29 hospitalized patients, which were significantly lower in severe cases, 87.7 μg/dL in mild and moderately ill patients (n = 22) and 62.4 μg/dL in severe cases (n = 7) [5]. If the cut off value is 70 μg/dL, the proportion of cases below the cut off value is 14% for mild and moderate cases and 86% for severe cases, and it is possible to predict the severity of the disease. Gonzalez et al. reported in a review of 249 hospitalized patients that the serum zinc level in 21 patients who died was 49 μg/dL, significantly lower than the 62 μg/dL level in surviving patients, and that the mortality rate in patients with serum zinc levels of less than 50 μg/dL on admission was 21%, higher than the 5% mortality rate in patients with serum levels of 50 μg/dL or higher [6]. Jothimani et al. reported that the median serum zinc level in 47 hospitalized patients was 74.5 μg/dL, which was lower than that in healthy subjects (105.8 μg/dL), that the level of less than 80 μg/dL was found in 57.4% of patients with a mortality rate of 18.5%, and that there were no deaths in patients with a level of 80 μg/dL or higher [7]. Dubourg et al. measured the serum zinc levels of 275 inpatients, and divided the cases of death, ICU admission, and hospitalization for 10 days or more into poor outcome cases (n=75), and the others into good outcome cases (n=200). The serum zinc level of poor outcome cases

was 84.1 μg/dL, which was significantly lower than the good outcome cases of 100.7 μg/dL [8]. Skalny et al. treated inpatients (n = 150) as mild (mean SpO_2: 95.4%, body temperature 38.2℃, CRP: 4.5mg/dL), moderate (mean SpO_2: 94.8%, body temperature 38.1℃, CRP: 6.7mg/dL) and severe (mean SpO_2: 87.0%, body temperature 38.3℃, CRP: 16.1 mg/dL), 50 cases each and 44 healthy subjects were examined, and the serum zinc level was 96 μg/dL in normal subjects, 92 μg/dL in mild subjects, 90 μg/dL in moderate subjects, and 87 μg/dL in severe subjects, and the Cu/Zn ratio increased with increasing severity [9]. From the above reports, it is considered that there is a correlation between the severity and the serum zinc level, but it is unclear whether zinc deficiency aggravates the disease or zinc decreases due to the aggravation, and further investigation is required.

From the relationship between COVID-19 and serum zinc level, zinc administration is clinically used for treatment, and its effect is expected. Finzi et al. reported that high doses of zinc, 138-184 mg/d, were administered orally to 4 COVID-19 cases, and clinical symptoms such as oxygen saturation and fever resolution improved, and the following year, they reported improvement in 28 clinical cases [19,20]. Derwand et al. also reported that 141 outpatients with COVID-19 treated with 50 mg/d of zinc, 400 mg/d of hydoroxychloroquine, and 500 mg/d of azithromycine for 5 days had a low hospitalization rate of 2.8% compared with 15.4% from general data, and a mortality rate was 0.7% compared with the general data of 3.4%, indicating the effectiveness of early treatment of infection [21]. However, Thomas et al. conducted a randomized control trial of 214 outpatients infected with SARS-CoV-2 in four groups: a control group, a zinc 50 mg group, a vitamin C 8000 mg group, and a zinc and vitamin C group [22]. The efficacy of zinc administration was not confirmed, as no relief was obtained between the 4 groups. Furthermore, in an RCT of hydroroxychloroquine with or without zinc, no add-on effect of zinc was confirmed [23]. Based on the results of these RCTs, the NIH does not recommend the administration of zinc in its treatment guidelines for COVID-19 [24]. Thus, the efficacy of zinc administration as adjuvant therapy in COVID-19 patients is controversial, and the results of future RCTs will be expected [25,26,27,28,29].

SARS-CoV-2 is known to be transmitted by the binding of spike protein to ACE 2 on the cell membrane in COVID-19 patients [30,31]. It has been reported that its expression is abundant in the epithelial cells of the nasal mucosa in addition to the epithelium of the airways, lungs, and intestines, suggesting an association with olfaction disorders [32]. Yan et al. performed PCR on 1480 patients with influenza-like symptoms and found that among 102 COVID-19 positive patients, 68% had olfactory disturbance and 71% had gustatory disturbance. In contrast, 16% of COVID-19-negative patients had olfactory disturbances and 17% had gustatory disturbances, indicating a strong association between COVID-19 and olfactory and gustatory disturbances, making it useful for screening [33]. Regarding the frequency of olfactory dysfunction, meta-analysis of 10 papers reported that dysosmia was found in 52.7% of 1627 cases, but there was a difference in the diagnosis depending on whether a validated instrument was used or not, 36.6% in nonvalidated cases and 86.6% in validated cases [34]. In our hospital, 35.3% of the patients were diagnosed by a simple interview, which was about the same frequency as that diagnosed by nonvalidated instrument. It has been reported that there are many females by gender, but no difference was found in our cases [35]. In terms of age, Alsheri reported a higher frequency in younger patients: 25/44 (56.8%) under 20 years of age, 14/28 (50.0%) in the 20-35 age group, 18/53 (34.0%) in the 35-60 age group, and 19/73 (26.0%) in the 60+ age group [36]. In our case, the average age of cases with dysosmia or dysgeusia was significantly younger (34.4 vs. 42.6 y/o), and the frequency of occurrence by age was 46.8% under 40 y/o and 17.5% over 40 y/o. In the relationship between dysosmia/dysgeusia and the severity of the disease, fewer patients with dysosmia or dysgeusia had pneumonia on CT (27.8 vs. 66.7%) and lower CRP than those without (0.32 vs. 0.87 mg/dL, p=0.06). Talavera et al. reported that 146 of 576 cases (25.3%) had anosmia, but those with anosmia were less frequently managed by the ICU and had a lower mortality rate [37]. Similarly, Foster et al. reported that cases of anosmia were less hospitalized and less likely to enter the ICU [38].

There has been only one publication on zinc and olfactory disturbances in COVID-19 patients, by Abdelmaksoud et al [11]. They found no difference in serum zinc levels, 61 μg/dL in patients without anosmia (n=54) and 59 μg/dL in patients with anosmia (n=80). Similarly, in our study, there was no difference in serum zinc levels between subjects with and without anosmia, and no association was found. However, Abdelmaksoud et al. reported that treatment with 100 mg/d of zinc significantly shortened the time to improvement from a median of 18 days without zinc to a median of 7 days with zinc.

This paper has a limitation. COVID-19 patients were assigned to hospitalization, hotel stay, or home treatment by the medical task force, and the criteria for inclusion in the study may have changed depending on the occurrence of patients. In addition, the time elapsed since the onset of the disease is not constant, and because this is a one-time test, the relationship with the subsequent course of the disease is unclear. Systematic testing and changes in the overall course of the disease need to be examined in the future.

Conclusion

An assessment of outpatients with SARS-CoV2 infection was performed. Most of the cases were mild, but 52.9% showed pneumonia on CT. The frequency of pneumonia findings increased with age. The serum zinc level of the cases was lower than that of healthy subjects, especially in those over 50 y/o. Serum zinc levels in patients with pneumonia findings were significantly lower than in those without pneumonia. Dysosmia or dysgeusia was found in 35.3% of patients but was not associated with serum zinc. Further data collection on the role of zinc in COVID-19 is needed.

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