Clinical clustering with prognostic implications in Japanese COVID-19 patients: report from Japan COVID-19 Task Force, a nation-wide consortium to investigate COVID-19 host genetics

Shiro Otake[1], Shotaro Chubachi[1*], Ho Namkoong[1], Kensuke Nakagawara[1], Hiromu Tanaka[1], Ho Lee[1], Atsuho Morita[1], Takahiro Fukushima[1], Mayuko Watase[1], Tatsuya Kusumoto[1], Katsunori Masaki[1], Hirofumi Kamata[1], Makoto Ishii[1], Naoki Hasegawa[2], Norihiro Harada[3], Tetsuya Ueda[4], Soichiro Ueda[5], Takashi Ishiguro[6], Ken Arimura[7], Fukuki Saito[8], Takashi Yoshiyama[9], Yasushi Nakano[10], Yoshikazu Mutoh[11], Yusuke Suzuki[12], Koji Murakami[13], Yukinori Okada[14], Ryuji Koike[15], Yuko Kitagawa[16], Akinori Kimura[17], Seiya Imoto[18], Satoru Miyano[19], Seishi Ogawa[20], Takanori Kanai[21], Koichi Fukunaga[1] and The Japan COVID-19 Task Force

Abstract

Background: The clinical course of coronavirus disease (COVID-19) is diverse, and the usefulness of phenotyping in predicting the severity or prognosis of the disease has been demonstrated overseas. This study aimed to investigate clinically meaningful phenotypes in Japanese COVID-19 patients using cluster analysis.

Methods: From April 2020 to May 2021, data from inpatients aged ≥ 18 years diagnosed with COVID-19 and who agreed to participate in the study were collected. A total of 1322 Japanese patients were included. Hierarchical cluster analysis was performed using variables reported to be associated with COVID-19 severity or prognosis, namely, age, sex, obesity, smoking history, hypertension, diabetes mellitus, malignancy, chronic obstructive pulmonary disease, hyperuricemia, cardiovascular disease, chronic liver disease, and chronic kidney disease.

Results: Participants were divided into four clusters: Cluster 1, young healthy (n = 266, 20.1%); Cluster 2, middle-aged (n = 245, 18.5%); Cluster 3, middle-aged obese (n = 435, 32.9%); and Cluster 4, elderly (n = 376, 28.4%). In Clusters 3 and 4, sore throat, dysosmia, and dysgeusia tended to be less frequent, while shortness of breath was more frequent. Serum lactate dehydrogenase, ferritin, KL-6, D-dimer, and C-reactive protein levels tended to be higher in Clusters 3 and 4. Although Cluster 3 had a similar age as Cluster 2, it tended to have poorer outcomes. Both Clusters 3 and 4 tended to exhibit higher rates of oxygen supplementation, intensive care unit admission, and mechanical ventilation, but the mortality rate tended to be lower in Cluster 3.

*Correspondence: bachibachi472000@live.jp

[1] Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, 35 Shinanomachi, Tokyo 160-8582, Japan
Full list of author information is available at the end of the article

Otake *et al. BMC Infectious Diseases* (2022) 22:735

Page 2 of 12

Conclusions: We have successfully performed the first phenotyping of COVID-19 patients in Japan, which is clinically useful in predicting important outcomes, despite the simplicity of the cluster analysis method that does not use complex variables.

Keywords: COVID-19, Pneumonia, Phenotype, Cluster analysis, Japan

Background

In December 2019, a disease outbreak was noticed after a massive admission of patients with common clinical symptoms of pneumonia in the local hospitals of Wuhan City, China. Upon further investigations, the World Health Organization confirmed that the novel coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was responsible for these clinical symptoms and further denominated this disease as coronavirus disease (COVID-19) [1]. Its clinical course is diverse, ranging from mild self-limited illness to life-threatening organ dysfunctions [2–4].

Identifying disease sub-phenotypes could improve the understanding of the pathophysiology of critical care syndromes and lead to the discovery of new treatment targets by allowing future therapeutic trials to focus on predicted responders [5]. COVID-19 cluster analysis was previously used to identify distinct sub-phenotypes based on clinical and biochemical characteristics [6–10], for other heterogeneous syndromes, such as acute respiratory distress syndrome, sepsis, and acute kidney injury [11]. However, the main factors in the cluster analysis and methodology differed among these studies, as did the characteristics of the sub-phenotypes. Moreover, most studies used not only baseline characteristics but also laboratory test results and radiographic patterns [7–10].

Previous reports, including ours, revealed that baseline characteristics, such as age, sex, and comorbidities, can predict meaningful outcomes of COVID-19 [12, 13]. The clinical characteristics of COVID-19 may differ depending on the population. For instance, COVID-19 is milder in Japan than in other countries [14, 15]. Population differences may be influenced by complex factors, including the number of patients, medical infrastructure, resources of medical personnel, and patient background [15]. To the best of our knowledge, no clinical studies to date have examined the phenotypes of COVID-19 patients in Japan.

Based on the above, we hypothesized that cluster analysis using baseline characteristics reportedly related to COVID-19 outcomes may allow for simple meaningful phenotyping of Japanese COVID-19 patients, and that sub-phenotypes may differ according to population differences and cluster analysis methods. The present study aimed to demonstrate the usefulness of phenotyping in predicting meaningful outcomes of Japanese COVID-19 patients and to capture the patients' post-hospitalization course.

Methods

Study design and settings

All COVID-19 cases in this retrospective cohort study were recruited through the Japan COVID-19 Task Force [16, 17]. From April 2020 to May 2021, data from consecutive inpatients aged ≥ 18 years diagnosed with COVID-19, using SARS-CoV2 polymerase chain reaction (PCR) test results at one among the >100 affiliated hospitals, and who agreed to cooperate in the study were registered in an electronic case record form by the study subspecialist at the affiliated research institute. Patients meeting any of the following exclusion criteria were excluded: (i) non-Japanese patients, (ii) patients with incomplete medical records, such as missing outcome information, and (iii) patients lacking any of the selected 12 variables for cluster analysis (Fig. 1). All patients provided written informed consent. This study was approved by the ethics committees of Keio University School of Medicine (20200061) and related research institutions. All aspects of the study conformed to the principles of the Declaration of Helsinki adopted by WMA General Assembly, Fortaleza, Brazil, October 2013.
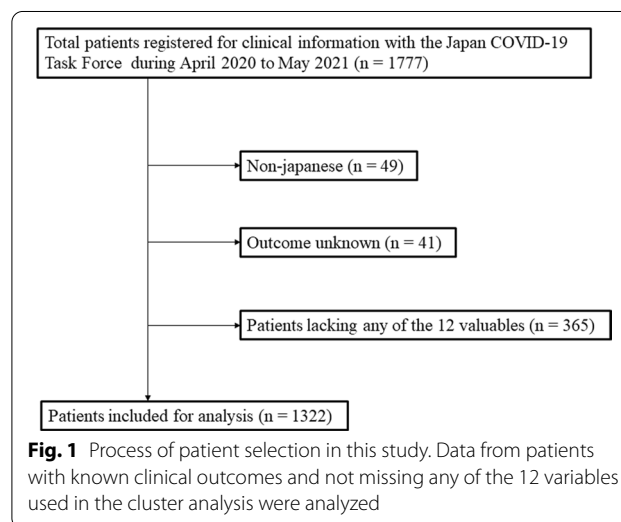
Fig. 1 Process of patient selection in this study. Data from patients with known clinical outcomes and not missing any of the 12 variables used in the cluster analysis were analyzed

Otake *et al. BMC Infectious Diseases*   (2022) 22:735

Page 3 of 12

Data collection

The following information was extracted from the electronic case record form: age, sex, height, weight, clinical symptoms and signs, laboratory findings on admission, comorbidities, disease severity (supplementary oxygen, intensive care unit (ICU) entry, need for invasive mechanical ventilation, and survival status), and treatment details. We defined disease severity as follows: most severe, need for support by high-flow oxygen devices, invasive mechanical ventilation, extracorporeal membrane oxygenation, or death; severe, need for support of low-flow oxygen devices; mild, symptomatic patients not requiring oxygen support; asymptomatic, asymptomatic patients without oxygen support [18]. All laboratory tests were performed according to the patients' clinical care needs. Symptoms and signs were included not only at the time of referral and admission, but also during hospitalization. Blood tests such as biochemistry, peripheral blood analysis, and coagulation were performed within 48 h of the initial visit or admission. The collected data were reviewed by a team of respiratory clinicians. If core data were missing, the clinician who first diagnosed the disease was contacted to collect it. Missing or absent data in the patient background were noted as unknown.

Identification of COVID-19 phenotypes using cluster analysis

We selected 12 clinically relevant patient baseline characteristics reportedly associated with the severity or prognosis of COVID-19 [12, 19–25], namely, age, sex, obesity, smoking history, hypertension, diabetes mellitus, malignancy, chronic obstructive pulmonary disease, hyperuricemia, cardiovascular disease, chronic liver disease, and chronic kidney disease. We defined obesity as body mass index (BMI) > 25 and treated it as a nominal variable.

Statistical analysis

Data are presented as means ± standard deviation (SD). Data were compared among groups using analysis of variance (ANOVA) and χ^2 tests. Hierarchical cluster analysis using the 12 variables mentioned above was performed using the Ward's minimum-variance method [26, 27]. The results are graphically depicted by a dendrogram. Statistical significance was set at $p < 0.05$. All data were analyzed using the JMP 16 software (SAS Institute, Cary, NC, USA).

Results

### Characteristics of the study population

Table 1 shows the baseline clinical characteristics of the participants. A total of 1322 inpatients (men, 65.1%;

Table 1 Baseline clinical characteristics of the study patients

n = 1322	
Age, years	58 ± 18.1
Male, n (%)	860 (65.1)
BMI, kg/m²	24.4 ± 4.7
Smoking history, n (%)	597 (45.2)
Hypertension, n (%)	449 (34)
Diabetes mellitus, n (%)	263 (19.9)
Malignancy, n (%)	99 (7.5)
COPD, n (%)	64 (4.8)
Hyperuricemia, n (%)	134 (10.1)
Cardiovascular disease, n (%)	114 (8.6)
Chronic liver disease, n (%)	43 (3.3)
Chronic kidney disease, n (%)	91 (6.9)

Data are shown as mean ± SD. Data were compared among groups using analysis of variance (ANOVA) and χ^2 tests

BMI, body mass index; COPD, chronic obstructive pulmonary disease
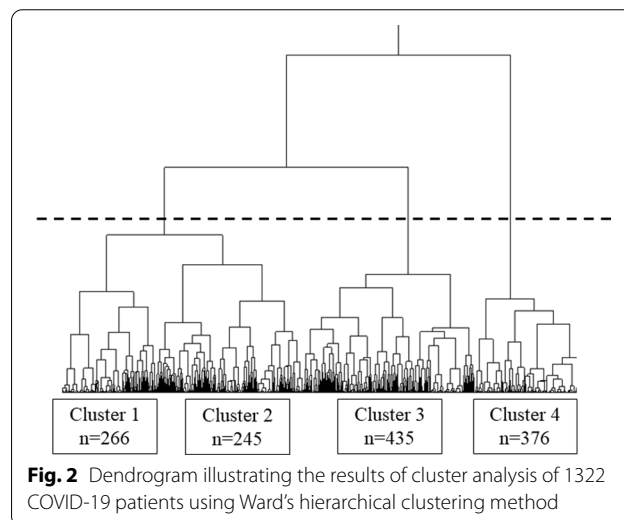
Fig. 2 Dendrogram illustrating the results of cluster analysis of 1322 COVID-19 patients using Ward's hierarchical clustering method

mean age, 58 ± 18.1 years) were enrolled in this study. The mean BMI was 24.4 ± 4.7 kg/m², and 597 (45.2%) had a history of smoking. Based on their clinical presentation, participants were classified into the most severe (n = 63, 4.8%), severe (n = 426, 32.2%), mild (n = 777, 58.8%), and asymptomatic (n = 56, 4.2%) disease groups. The most common comorbidities were hypertension (n = 449, 34%), diabetes mellitus (n = 263, 19.9%), and hyperuricemia (n = 134, 10.1%).

Comparison of baseline characteristics among clusters

We performed Ward's cluster analysis based on 12 factors reportedly associated with the severity or prognosis of COVID-19 [12, 19–25]. Based on visual assessment

Otake *et al. BMC Infectious Diseases* (2022) 22:735

Page 4 of 12

of the resulting dendrogram (Fig. 2), data could be optimally grouped into four clusters, with each cluster corresponding to a potential phenotype. Table 2 presents the baseline characteristics of each cluster. Cluster 1 (young healthy cluster: n = 266) included the youngest population and tended to have fewer comorbidities than the other clusters. Cluster 3 (middle-aged obese cluster: n = 435) included mostly middle-aged patients, had the highest percentage of men with higher BMI and numerous comorbidities, such as hypertension, diabetes mellitus, and hyperuricemia. Although patients in Cluster 2 (middle-aged cluster: n = 245) were in the same age group as those in Cluster 3, they tended to have a lower BMI and fewer comorbidities compared to those in Cluster 3. Compared to other clusters, Cluster 4 (elderly: n = 376) included the oldest patients who tended to have numerous comorbidities, such as malignancy, cardiovascular diseases, and chronic kidney disease.

Comparison of clinical characteristics and laboratory findings among clusters

Table 3 shows a comparison of the subjective symptoms and physical findings among the four clusters. Sore throat, dysosmia, and dysgeusia, all reported as good prognostic factors [12, 28, 29], tended to be more frequent in Cluster 1 than in other clusters. In contrast, shortness of breath, reported as a poor prognostic factor [30], tended to be less frequent in Cluster 1 than in other clusters. Cluster 4 exhibited the lowest prevalence of sore throat, dysosmia, and dysgeusia among the four clusters, but more frequent consciousness disturbance, reportedly a poor prognostic factor [31],

than other clusters. Table 4 shows a comparison of the laboratory findings among the clusters. Platelet count, reported as a poor prognostic factor [32], tended to be lower in Clusters 3 and 4, while lactate dehydrogenase (LDH), ferritin, Krebs von den Lungen-6 (KL-6), D-dimer, and C-reactive protein (CRP), also considered poor prognostic factors [33–35], tended to be lower in Cluster 1 and higher in Clusters 3 and 4. These results imply that Cluster 1 had COVID-19 related symptoms and laboratory findings associated with good prognosis, while Clusters 3 and 4 had poor prognosis.

Comparison of clinical outcomes between the four clusters

A comparison of the rate of supplemental oxygen needs, ICU admission, mechanical ventilation, and mortality is shown in Fig. 3. Cluster 3 exhibited a higher rate of patient receiving supplementary oxygen and/or mechanical ventilation, admitted to the ICU, and mortality compared to Clusters 1 and 2. Cluster 2 had intermediate rates of the above factors, between Clusters 1 and 3, and Cluster 1 exhibited the most favorable outcomes among all the clusters. Similar to Cluster 3, Cluster 4 also tended to have poor outcomes, coupled with a higher mortality rate. These results suggest that middle-aged obese men tend to have a similarly serious course as the elderly but with a lower risk of death. Consistent with the high rate of severe disease in Clusters 3 and 4, patients in these clusters received intensive drug treatment, including remdesivir and glucocorticoids, of current frequent use and considered to be effective in the treatment of COVID-19 [36] (Table 5).

Table 2 Baseline characteristics for each cluster

	Cluster 1 Young healthy n = 266	Cluster 2 Middle aged n = 245	Cluster 3 Middle aged obese n = 435	Cluster 4 Elderly n = 376	p-value
Age, years	31.7 ± 0.6	61.1 ± 0.6	56.9 ± 0.5	76.1 ± 0.5	< 0.0001
Male, n (%)	135 (50.8)	180 (73.5)	364 (83.7)	181 (48.1)	< 0.0001
BMI, kg/m^2	22.9 ± 0.2	22 ± 0.2	28.3 ± 0.2	22.3 ± 0.2	< 0.0001
Smoking history, n (%)	99 (37.2)	117 (47.8)	247 (56.8)	134 (35.6)	< 0.0001
Hypertension, n (%)	0 (0)	13 (5.3)	206 (47.4)	230 (61.2)	< 0.0001
Diabetes mellitus, n (%)	2 (0.8)	56 (22.9)	124 (28.5)	81 (21.5)	< 0.0001
Malignancy, n (%)	6 (2.3)	13 (5.3)	18 (4.1)	62 (16.5)	< 0.0001
COPD, n (%)	0 (0)	31 (12.7)	16 (3.7)	17 (4.5)	< 0.0001
Hyperuricemia, n (%)	4 (1.5)	4 (1.6)	98 (22.5)	28 (7.5)	< 0.0001
Cardiovascular disease, n (%)	1 (0.4)	1 (0.4)	47 (10.8)	65 (17.3)	< 0.0001
Chronic liver disease, n (%)	0 (0)	4 (1.6)	29 (6.7)	10 (2.7)	< 0.0001
Chronic kidney disease, n (%)	1 (0.4)	14 (5.7)	34 (7.8)	42 (11.2)	< 0.0001

Data are shown as mean ± SD. Data were compared among groups using analysis of variance (ANOVA) and χ^2 tests

BMI, body mass index; COPD, chronic obstructive pulmonary disease

Otake *et al. BMC Infectious Diseases* (2022) 22:735

Page 5 of 12

Table 3 Comparison of subjective symptoms and physical findings among the four clusters

	Cluster 1 Young healthy	Cluster 2 Middle aged	Cluster 3 Middle aged obese	Cluster 4 Elderly	p-value
Consciousness disturbance, n (%)	1 (0.4)	4 (1.6)	3 (0.7)	16 (4.3)	0.0004
Cough, n (%)	140 (52.8)	158 (64.5)	283 (66)	198 (53.2)	0.0001
Sputum, n (%)	47 (17.7)	59 (24.5)	112 (25.9)	78 (21)	0.0634
Sore throat, n (%)	91 (35)	63 (26)	115 (26.6)	64 (17.3)	< 0.0001
Nasal discharge, n (%)	62 (23.7)	43 (17.7)	71 (16.4)	46 (12.4)	0.0029
Taste disorder, n (%)	86 (33.3)	39 (16)	75 (17.4)	39 (10.5)	< 0.0001
Smell disorder, n (%)	90 (34.9)	32 (13.1)	70 (16.3)	25 (6.7)	< 0.0001
Shortness of breath, n (%)	52 (20.4)	65 (27.1)	140 (32.6)	93 (25.4)	0.005
Malaise, n (%)	105 (39.8)	113 (46.3)	225 (52.3)	147 (39.7)	0.0009
Body temperature $\geqq$ 37.5 °C, n (%)	186 (70.5)	213 (86.9)	370 (86.1)	260 (69.9)	< 0.0001
Systolic pressure, mmHg	120 ± 1.2	129.4 ± 1.2	131.6 ± 0.9	132 ± 1	< 0.0001
Diastolic pressure, mmHg	78.5 ± 0.8	81.4 ± 0.8	85.1 ± 0.6	77.7 ± 0.7	< 0.0001
Heart rate, bpm	84.4 ± 1	88.6 ± 1	90 ± 0.8	84.3 ± 0.8	< 0.0001
Respiratory rate, bpm	17.5 ± 0.3	19.3 ± 0.3	19.4 ± 0.2	19 ± 0.2	< 0.0001
SpO$_2$, %	97.6 ± 0.2	96.3 ± 0.2	95.9 ± 0.1	95.5 ± 0.1	< 0.0001

Data are shown as mean ± SD. Data were compared among groups using analysis of variance (ANOVA) and χ^2 tests

SpO$_2$, saturation of percutaneous oxygen

Discussion

This study was the first in Japan to perform a cluster analysis of COVID-19 patients. We identified four clinical sub-phenotypes, namely the "young healthy cluster" (Cluster 1), "middle-aged cluster" (Cluster 2), "middle-aged obese cluster" (Cluster 3), and "elderly cluster" (Cluster 4), which were associated with different outcomes in Japanese patients with COVID-19. Previous reports, including ours, have shown that comorbidities and mortality rates in Japan differed from inpatient studies in other countries [15, 17]. Thus, the identification of the meaningful sub-phenotypes of Japanese COVID-19 patients is important. Notably, our study used simple baseline characteristics as variables for cluster analysis. Several previous studies have shown that cluster analysis is useful for phenotyping and predicting COVID-19 outcomes [6–10]. However, most of these studies used complicated variables, combining a wide range of blood test results for clustering. Promptly indefinable is an important feature for defining COVID-19 sub-phenotypes [37]. We believe that the present simple clustering may be of great help to clinicians in predicting prognosis and performing individualized therapy.

Cluster 3 included mainly middle-aged patients with a high BMI, and a high rate of complications from lifestyle-related diseases, such as hypertension, diabetes, and hyperuricemia. Even though hyperuricemia has been previously reported to be associated with prognosis [38, 39], its rate was higher in Cluster 3

than in Cluster 4, which showed the highest mortality rate. This finding may be due to a possible association between obesity and hyperuricemia [40, 41]. Cluster 2 patients were similarly middle-aged but had lower BMI and lifestyle-related diseases. Cluster 3 revealed poorer outcomes, including need for oxygen, ICU admission, and intubation, than Cluster 2. This result is consistent with the fact that obesity has already been reported as a poor prognostic factor for COVID-19 [20], as have lifestyle-related diseases [12, 21, 22]. However, the mortality rate of Cluster 3 was lower than that of Cluster 4. Despite the high risk of severe disease, there is still life-saving potential, suggesting that this cluster is likely to benefit from aggressive intensive care.

Cluster 1 consisted mainly of younger patients with fewer comorbidities. They showed the highest frequency of sore throat, dysosmia, and dysgeusia of all the clusters, and the outcomes were generally the most favorable. These results were consistent with previous reports showing that upper respiratory tract symptoms are related to a good prognosis. [12, 28, 29]. In addition, several biomarkers (LDH, ferritin, KL-6, D-dimer, and CRP) [33–35] reported as poor prognosis predictors were lower in Cluster 1 than in other clusters. A majority of young people with COVID-19 are reported to be asymptomatic or have few symptoms [42], and this cluster also tended to have fewer symptoms than other clusters, except for upper respiratory tract symptoms. It is possible that this group may have contributed to the spread of the disease.

Otake *et al. BMC Infectious Diseases* (2022) 22:735

Page 6 of 12

Table 4 Comparison of laboratory findings among the four clusters

	Cluster 1 Young healthy	Cluster 2 Middle aged	Cluster 3 Middle aged obese	Cluster 4 Elderly	p-value
WBC, /μL	4854.2 ± 141	5530.2 ± 146.4	5531.3 ± 110	5553.9 ± 118.8	0.0003
Lymphocyte, %	28.9 ± 0.7	19.9 ± 0.8	22.9 ± 0.6	21.1 ± 0.6	< 0.0001
Lymphocyte, /μL	1317.6 ± 38.8	1146.1 ± 26	1105 ± 40.8	1048.8 ± 24.2	< 0.0001
Hb, g/dL	14.5 ± 0.1	14.2 ± 0.1	14.8 ± 0.1	12.9 ± 0.1	< 0.0001
PLT, × 10^4/μL	21.9 ± 0.5	19.8 ± 0.5	19.3 ± 0.4	19 ± 0.4	< 0.0001
Alb, g/dL	4.3 ± 0.03	3.8 ± 0.03	3.8 ± 0.02	3.5 ± 0.03	< 0.0001
TB, mg/dL	0.6 ± 0.03	0.7 ± 0.03	0.7 ± 0.02	0.6 ± 0.02	0.0104
ALP, U/L	154.5 ± 8.4	163.5 ± 8.6	178.2 ± 6.5	188.3 ± 6.9	0.0091
γGTP, U/L	41.5 ± 5.3	66.5 ± 5.5	92.3 ± 4.1	48.5 ± 4.4	< 0.0001
AST, U/L	26.6 ± 2	41.7 ± 2.1	45.2 ± 1.6	36 ± 1.7	< 0.0001
ALT, U/L	28.8 ± 2.1	33.9 ± 2.2	49.7 ± 1.6	26.6 ± 1.7	< 0.0001
BUN, mg/dL	10.8 ± 0.9	16.7 ± 0.9	15.9 ± 0.7	21.1 ± 0.7	< 0.0001
Cr, mg/dL	0.7 ± 0.1	1.3 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	0.0006
LDH, U/L	193.8 ± 5.9	267.7 ± 6.1	272.3 ± 4.6	266 ± 4.9	< 0.0001
UA, mg/dL	4.7 ± 0.1	4.6 ± 0.1	5.2 ± 0.1	4.9 ± 0.1	< 0.0001
CK, U/L	93.9 ± 31.7	226.4 ± 32.8	152.1 ± 24.3	154 ± 26.2	0.0375
Na, mEq/L	140.1 ± 0.2	137.7 ± 0.2	137.8 ± 0.2	137.9 ± 0.2	< 0.0001
K, mEq/L	4 ± 0.03	4 ± 0.03	4 ± 0.02	4 ± 0.02	0.4417
Cl, mEq/L	103.5 ± 0.2	101.1 ± 0.3	101 ± 0.2	101.9 ± 0.2	< 0.0001
TroponinT, ng/mL	0.1 ± 1	1.2 ± 1.1	0.6 ± 0.8	2.4 ± 0.9	0.2919
BNP, pg/mL	7.5 ± 19.1	33.5 ± 15.7	31.4 ± 12.4	86.1 ± 13.8	0.0025
IgG, mg/dL	1197.4 ± 25.4	1184 ± 27.3	1208.2 ± 18.7	1231.6 ± 21	0.5306
IgA, mg/dL	231.9 ± 10.4	252.1 ± 11.4	287.2 ± 7.6	264.1 ± 8.5	0.0002
IgM, mg/dL	108.5 ± 4.6	82.5 ± 5	87.5 ± 3.3	85 ± 3.8	0.0001
C3, mg/dL	120.9 ± 4.1	123.4 ± 3.8	138.8 ± 2.5	111.7 ± 3.1	< 0.0001
C4, mg/dL	34.5 ± 1.9	39.9 ± 1.8	43.4 ± 1.2	34.7 ± 1.4	< 0.0001
CH50, U/mL	56.8 ± 5	73.2 ± 5.3	75.8 ± 3.2	63.8 ± 3.2	0.0053
Ferritin, ng/mL	240.7 ± 33.4	533.3 ± 35.1	655.4 ± 25.8	412.7 ± 28.6	< 0.0001
TG, mg/dL	115.5 ± 10.8	114.6 ± 11.1	159.3 ± 7.6	108 ± 8.5	< 0.0001
KL-6, U/mL	199.3 ± 16.1	273.4 ± 16.7	307.1 ± 12.4	356.2 ± 13.3	< 0.0001
HbA1c, %	5.5 ± 0.1	6.3 ± 0.1	6.7 ± 0.1	6.3 ± 0.1	< 0.0001
APTT, sec	33.6 ± 0.6	34.5 ± 0.6	34.2 ± 0.4	36.1 ± 0.5	0.0019
PT-INR	1 ± 0.01	1 ± 0.01	1 ± 0.01	1.1 ± 0.01	0.0061
Fibrinogen, mg/dL	363.7 ± 9.7	514.9 ± 10.1	514.6 ± 7.2	475.8 ± 7.8	< 0.0001
ᴅ-dimer, μg/mL	0.8 ± 0.4	1.7 ± 0.4	1.5 ± 0.3	2.8 ± 0.3	< 0.0001
Procalcitonin, ng/mL	0.1 ± 0.1	0.3 ± 0.1	0.1 ± 0.1	0.3 ± 0.1	0.0835
CRP, mg/dL	1.1 ± 0.3	5 ± 0.3	5 ± 0.2	4.7 ± 0.2	< 0.0001

Data are shown as mean ± SD. Data were compared among groups using analysis of variance (ANOVA)

WBC, white blood cell; Hb, hemoglobin; PLT, platelet; Alb, albumin; TB, total bilirubin; ALP, alkaline phosphatase; γGTP, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; LDH, lactate dehydrogenase; UA, uric acid; CK, creatinine kinase; Na, sodium; K, potassium; Cl, chlorine; BNP, brain natriuretic peptide; TG, triglyceride; KL-6, Krebs von den Lungen-6; APTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; CRP, C-reactive protein

Cluster 4 included predominantly older patients with comorbidities such as hypertension, diabetes, malignant disease, cardiovascular disease, and chronic kidney disease. They had the poorest outcomes in terms of oxygen demand, ICU admission, ventilator use, and death. These results were consistent with previous reports showing that old age and comorbidities are related with poor prognosis [12, 19, 21–24]. In addition, several poor prognostic biomarkers (LDH, ferritin, KL-6, ᴅ-dimer, and CRP) [33–35] were higher than those in Clusters 1 and 2. Lymphocyte count, which has been linked to severe disease and mortality,

Fig. 3 Comparison of clinical outcomes among the four clusters. **a** Comparison of the rate of receiving supplementary oxygen. **b** Comparison of the rate of ICU admission. **c** Comparison of the rate of requiring mechanical ventilation. **d** Comparison of the mortality rate. *p < 0.05 and **p < 0.005
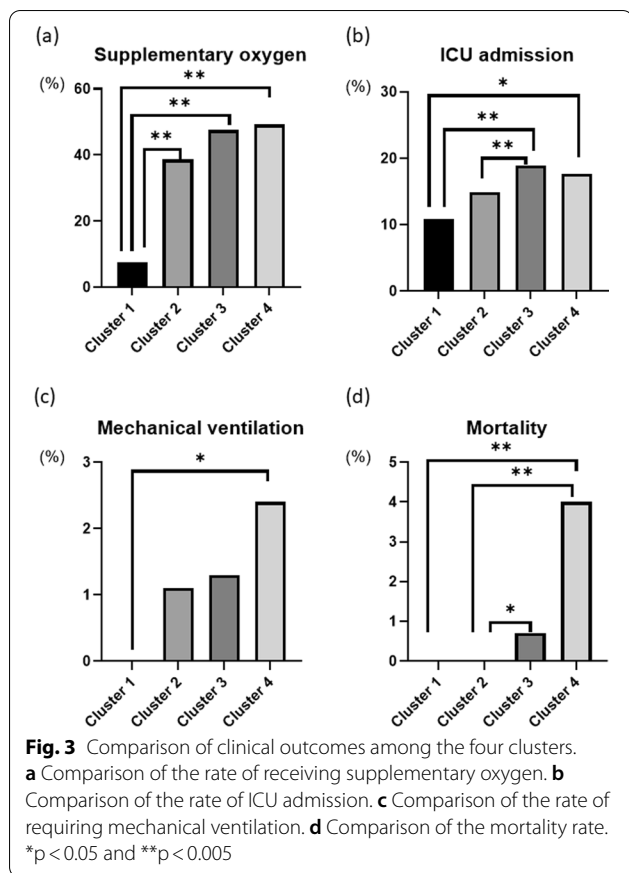
was also lowest in Cluster 4 [43]. The mechanism of this lymphocytopenia has been previously reported to be hypercytokinemia, leading to inhibition of hematopoiesis by TNF-α [44]. In fact, Cluster 4 patients with low lymphocyte count also showed a trend toward low hemoglobin level and platelet count, consistent with previous reports. Among patients in Cluster 4, 4% were

admitted to the ICU and 17.6% of intubated patients died, indicating their potential as a target for future development of COVID-19 therapy.

One of the characteristics of the present study is the inclusion of a single racial group only. Many of the previous studies on cluster analysis of COVID-19 patients included multiple racial groups in their analyses [6, 7], and each cluster had different proportions of racial groups, suggesting that the clinical characteristics also reflect the racial differences. In contrast, since only Japanese patients were analyzed in this study, we focused more on basic clinical information, such as age, weight, and comorbidities, and the characteristics of the clusters can be easily grasped.

Some potential limitations of our study need to be discussed. First, the phenotyping of infectious diseases requires consideration of both the host and pathogen. SARS-CoV-2 is prone to genetic evolution, resulting in multiple variants with different characteristics compared to ancestral strains. Specifically, the transmissibility and virulence of these variants can greatly differ [45]. However, our study had no detailed data on viral load and/or strain. Second, we had no validation cohort data, necessitating additional studies. Third, we could not compare the differences in treatment response among the clusters. Five essential criteria could help define COVID-19 subtypes: (1) biologically plausible, (2) promptly identifiable, (3) nonsynonymous, (4) reproducible, and most importantly, (5) treatment responsive. To establish precision medicine against COVID-19 disease, further studies with more detailed and representative data are warranted.

Conclusions
We developed a simplified tool for clustering COVID-19 patients with diverse characteristics into sub-phenotypes. We identified four clusters that predicted

Table 5 Comparison of drug treatment among the four clusters

	Cluster 1 Young healthy	Cluster 2 Middle aged	Cluster 3 Middle aged obese	Cluster 4 Elderly	p-value
Antibiotics, n (%)	17 (6.5)	49 (20.3)	83 (19.2)	90 (24.1)	< 0.0001
Azithromycin, n (%)	21 (7.9)	29 (12)	50 (11.6)	63 (16.9)	0.0066
Ciclesonide, n (%)	35 (13.3)	48 (19.9)	77 (17.9)	52 (14)	0.0957
Favipiravir, n (%)	29 (10.9)	92 (38)	168 (38.8)	130 (34.8)	< 0.0001
Hydroxychloroquine, n (%)	0 (0)	2 (0.8)	2 (0.5)	2 (0.5)	0.5759
Lopinavir and Ritonavir, n (%)	1 (0.4)	2 (0.8)	0 (0)	2 (0.5)	0.3684
Remdesivir, n (%)	10 (3.8)	53 (22)	85 (19.8)	68 (18.5)	< 0.0001
Nafamostat, n (%)	3 (1.1)	15 (6.2)	39 (9.1)	26 (7.1)	< 0.0001
Anticoagulant, n (%)	15 (5.6)	48 (19.8)	86 (19.9)	98 (26.1)	< 0.0001
Glucocorticoids, n (%)	25 (9.4)	100 (40.8)	219 (50.6)	179 (48)	< 0.0001

Data were compared among groups using χ^2 tests

Otake *et al. BMC Infectious Diseases* (2022) 22:735

Page 8 of 12

in-hospital outcomes in a large nationwide series of Japanese COVID-19 patients. This simple clustering will be of great help to clinicians in predicting prognosis and performing individualized therapy. Further studies are needed to develop precision medicine for COVID-19.

Abbreviations
PCR: Polymerase chain reaction; ICU: Intensive care unit; BMI: Body mass index; SD: Standard deviation; LDH: Lactate dehydrogenase; KL-6: Krebs von den Lungen-6; CRP: C-reactive protein; COVID-19: Coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Takahiro Fukushima[1], Shotaro Chubachi[1], Ho Namkoong[1], Shiro Otake[1], Kensuke Nakagawara[1], Hiromu Tanaka[1], Ho Lee[1], Atsuho Morita[1], Mayuko Watase[1], Takuya Kusumoto[1], Katsunori Masaki[1], Hiroki Kabata[1], Hirofumi Kamata[1], Makoto Ishii[1], Naoki Hasegawa[2], Kazuhisa Takahashi[3], Norihiro Harada[3], Toshio Naito[4], Makoto Hiki[5,6], Yasushi Matsushita[7], Haruhi Takagi[3], Ryousuke Aoki[8], Ai Nakamura[3], Sonoko Harada[3,9], Hitoshi Sasano[3], Shinnosuke Ikemura[1], Satoshi Okamori[1], Hideki Terai[1], Takanori Asakura[1], Junichi Sasaki[10], Hiroshi Morisaki[11], Yoshifumi Uwamino[12], Kosaku Nanki[13], Yohei Mikami[13], Sho Uchida[2], Shunsuke Uno[2], Rino Ishihara[13], Yuta Matsubara[13], Tomoyasu Nishimura[2,14], Takunori Ogawa[1], Toshiro Sato[15], Tetsuya Ueda[16], Masanori Azuma[16], Ryuichi Saito[16], Toshikatsu Sado[16], Yoshimune Miyazaki[16], Ryuichi Sato[16], Yuki Haruta[16], Tadao Nagasaki[16], Yoshinori Yasui[17], Yoshinori Hasegawa[16], Soichiro Ueda[18], Ai Tada[18], Masayoshi Miyawaki[18], Masaomi Yamamoto[18], Eriko Yoshida[18], Reina Hayashi[18], Tomoki Nagasaka[18], Sawako Arai[18], Yutaro Kaneko[18], Kana Sasaki[18], Takashi Ishiguro[19], Taisuke Isono[19], Shun Shibata[19], Yuma Matsui[19], Chiaki Hosoda[19], Kenji Takano[19], Takashi Nishida[19], Yoichi Kobayashi[19], Yotaro Takaku[19], Noboru Takayanagi[19], Etsuko Tagaya[20], Masatoshi Kawana[21], Ken Arimura[20], Yasushi Nakamori[22], Kazuhisa Yoshiya[22], Fukuki Saito[22], Tomoyuki Yoshihara[22], Daiki Wada[22], Hiromu Iwamura[22], Syuji Kanayama[22], Shuhei Maruyama[22], Takanori Hasegawa[23], Kunihiko Takahashi[23], Tatsuhiko Anzai[23], Satoshi Ito[23], Akifumi Endo[24], Yuji Uchimura[25], Yasunari Miyazaki[26], Takayuki Honda[26], Tomoya Tateishi[26], Shuji Tohda[27], Naoya Ichimura[27], Kazunari Sonobe[27], Chihiro Tani Sassa[27], Jun Nakajima[27], Masumi Ai[28], Takashi Yoshiyama[29], Ken Ohta[29], Hiroyuki Kokuto[29], Hideo Ogata[29], Yoshiaki Tanaka[29], Kenichi Arakawa[29], Masafumi Shimoda[29], Takeshi Osawa[29], Yasushi Nakano[30], Yukiko Nakajima[30], Ryusuke Anan[30], Ryosuke Arai[30], Yuko Kurihara[30], Yuko Harada[30], Kazumi Nishio[30], Yoshikazu Mutoh[31], Tomonori Sato[32], Reoto Takei[32], Satoshi Hagimoto[32], Yoichiro Noguchi[32], Yasuhiko Yamano[32], Hajime Sasano[32], Sho Ota[32], Yusuke Suzuki[33], Sohei Nakayama[33], Keita Masuzawa[33], Tomomi Takano[34], Kazuhiko Katayama[35], Koji Murakami[36], Mitsuhiro Yamada[36], Hisatoshi Sugiura[36], Hirohito Sano[36], Shuichiro Matsumoto[36], Nozomu Kimura[36], Yoshinao Ono[36], Hiroaki Baba[37], Rie Baba[38], Daisuke Arai[38], Takayuki Ogura[38], Hidenori Takahashi[38], Shigehiro Hagiwara[38], Genta Nagao[38], Shunichiro Konishi[38], Ichiro Nakachi[38], Hiroki Tateno[39], Isano Hase[39], Shuichi Yoshida[39], Shoji Suzuki[39], Miki Kawada[40], Hirohisa Horinouchi[41], Fumitake Saito[42], Keiko Mitamura[43], Masao Hagihara[44], Junichi Ochi[42], Tomoyuki Uchida[44], Ryuya Edahiro[45,46], Yuya Shirai[45,46], Kyuto Sonehara[46,47], Tatsuhiko Naito[46], Kenichi Yamamoto[46], Shinichi Namba[46], Ken Suzuki[46], Takayuki Shiroyama[45], Yuichi Maeda[45], Takuro Nii[45], Yoshimi Noda[45], Takayuki Niitsu[45], Yuichi Adachi[45], Takatoshi Enomoto[45], Saori Amiya[45], Reina Hara[45], Toshihiro Kishikawa[46,48,50], Shuhei Yamada[49], Shuhei Kawabata[49], Noriyuki Kijima[49], Masatoshi Takagaki[49,54], Noa Sasa[46,48], Yuya Ueno[48], Motoyuki Suzuki[48], Norihiko Takemoto[48], Hirotaka Eguchi[48], Takahito Fukusumi[48], Takao Imai[48], Munehisa Fukushima[48,53], Haruhiko Kishima[49], Hidenori Inohara[48], Kazunori Tomono[51], Kazuto Kato[52], Haruhiko Hirata[45], Yoshito Takeda[45], Atsushi Kumanogoh[45,47,54,55], Naoki Miyazawa[56], Yasuhiro Kimura[56], Reiko Sado[56], Hideyasu Sugimoto[56], Akane Kamiya[57], Naota Kuwahara[58], Akiko Fujiwara[58], Tomohiro Matsunaga[58], Yoko Sato[58], Takenori Okada[58], Takashi Inoue[59], Toshiyuki Hirano[59], Keigo Kobayashi[59], Hatsuyo Takaoka[59], Koichi Nishi[60], Masaru Nishitsuji[60], Mayuko Tani[60], Junya Suzuki[60], Hiroki Nakatsumi[60], Hidefumi Koh[61], Tadashi Manabe[61], Yohei Funatsu[61], Fumimaro Ito[61], Takahiro Fukui[61], Keisuke Shinozuka[61], Sumiko Kohashi[61], Masatoshi Miyazaki[61], Tomohisa Shoko[62], Mitsuaki Kojima[62], Tomohiro Adachi[63], Motonao Ishikawa[63], Kenichiro Takahashi[64], Kazuyoshi Watanabe[65], Yoshihiro Hirai[66], Hidetoshi Kawashima[66], Atsuya Narita[66], Kazuki Niwa[67], Yoshiyuki Sekikawa[67], Hisako Sageshima[68], Yoshihiko Nakamura[69], Kota Hoshino[69], Junichi Maruyama[69], Hiroyuki Ishikura[69], Tohru Takata[70], Takashi Ogura[71], Hideya Kitamura[71], Eri Hagiwara[71], Kota Murohashi[71], Hiroko Okabayashi[71], Takao Mochimaru[72,73], Shigenari Nukaga[72], Ryosuke Satomi[72,] Yoshitaka Oyamada[73], Nobuaki Mori[74], Tomoya Baba[75], Yasutaka Fukui[75], Mitsuru Odate[75], Shuko Mashimo[75], Yasushi Makino[75], Kazuma Yagi[76], Mizuha Hashiguchi[76], Junko Kagyo[76], Tetsuya Shiomi[76], Kodai Kawamura[77], Kazuya Ichikado[77], Kenta Nishiyama[77], Hiroyuki Muranaka[77], Kazunori Nakamura[77], Satoshi Fuke[78], Hiroshi Saito[78], Tomoya Tsuchida[79], Shigeki Fujitani[80], Mumon Takita[80], Daiki Morikawa[80], Toru Yoshida[80], Takehiro Izumo[81], Minoru Inomata[81], Naoyuki Kuse[81], Nobuyasu Awano[81], Mari Tone[81], Akihiro Ito[82], Toshio Odani[83], Masaru Amishima[84], Takeshi Hattori[84], Yasuo Shichinohe[85], Takashi Kagaya[86], Toshiyuki Kita[86], Kazuhide Ohta[86], Satoru Sakagami[86], Kiyoshi Koshida[86], Morio Nakamura[86], Koutaro Yokote[87], Taka-Aki Nakada[88], Ryuzo Abe[88], Taku Oshima[88], Tadanaga Shimada[88], Kentaro Hayashi[89], Tetsuo Shimizu[89], Yutaka Kozu[89], Hisato Hiranuma[89], Yasuhiro Gon[89], Namiki Izumi[90], Kaoru Nagata[90], Ken Ueda[90], Reiko Taki[90], Satoko Hanada[90], Naozumi Hashimoto[91], Keiko Wakahara[91], Koji Sakamoto[91], Norihito Omote[91], Akira Ando[91], Yu Kusaka[92], Takehiko Ohba[92], Susumu Isogai[92], Aki Ogawa[92], Takuya Inoue[92], Nobuhiro Kodama[93], Yasunari Kaneyama[93], Shunsuke Maeda[93], Takashige Kuraki[94], Takemasa Matsumoto[94], Masahiro Harada[95], Takeshi Takahashi[95], Hiroshi Ono[95], Toshihiro Sakurai[95], Takayuki Shibusawa[95], Yusuke Kawamura[96], Akiyoshi Nakayama[96], Hirotaka Matsuo[96], Yoshifumi Kimizuka[97], Akihiko Kawana[97], Tomoya Sano[97], Chie Watanabe[97], Ryohei Suematsu[97], Makoto Masuda[98], Aya Wakabayashi[98], Hiroki Watanabe[98], Suguru Ueda[98], Masanori Nishikawa[98,] Ayumi Yoshifuji[99], Kazuto Ito[99], Saeko Takahashi[100], Kota Ishioka[100], Yusuke Chihara[101], Mayumi Takeuchi[101], Keisuke Onoi[101], Jun Shinozuka[101], Atsushi Sueyoshi[101], Yoji Nagasaki[102], Masaki Okamoto[103,104], Sayoko Ishihara[105], Masatoshi Shimo[105], Yoshihisa Tokunaga[103,104], Masafumi Watanabe[106], Sumito Inoue[106], Akira Igarashi[106], Masamichi Sato[106], Nobuyuki Hizawa[107], Yoshiaki Inoue[108], Shigeru Chiba[109], Kunihiro Yamagata[110], Yuji Hiramatsu[111], Hirayasu Kai[110], Satoru Fukuyama[112], Yoshihiro Eriguchi[113], Akiko Yonekawa[113], Keiko Kan-o[112], Koichiro Matsumoto[112], Kensuke Kanaoka[114], Shoichi Ihara[114], Kiyoshi Komuta[114], Koichiro Asano[115], Tsuyoshi Oguma[115], Yoko Ito[115], Satoru Hashimoto[116], Masaki Yamasaki[116], Yu Kasamatsu[117], Yuko Komase[118], Naoya Hida[118], Takahiro Tsuburai[118], Baku Oyama[118], Yuichiro Kitagawa[119], Tetsuya Fukuta[119], Takahito Miyake[119], Shozo Yoshida[119], Shinji Ogura[119], Minoru Takada[120], Hidenori Kanda[120], Shinji Abe[121], Yuta Kono[121], Yuki Togashi[121], Hiroyuki Takoi[121], Ryota Kikuchi[121], Shinichi Ogawa[122], Tomouki Ogata[122], Shoichiro Ishihara[122], Arihiko Kanehiro[123,124], Shinji Ozaki[123], Yasuko Fuchimoto[123], Sae Wada[123], Nobukazu Fujimoto[124], Kei Nishiyama[125], Mariko Terashima[126], Satoru Beppu[126], Kosuke Yoshida[126], Osamu Narumoto[127], Hideaki Nagai[127], Nobuharu Ooshima[127], Mitsuru Motegi[128], Akira Umeda[129], Kazuya Miyagawa[130], Hisato Shimada[131], Mayu Endo[132], Yoshiyuki Ohira[133], Hironori Sagara[133], Akihiko Tanaka[133], Shin Ohta[133], Tomoyuki Kimura[133], Yoko Shibata[134], Yoshinori Tanino[134], Takefumi Nikaido[134], Hiroyuki Minemura[134], Yuki Sato[134], Yuichiro Yamada[135], Takuya Hashino[135], Masato Shinoki[135], Hajime Iwagoe[136], Hiroshi Takahashi[137], Kazuhiko Fujii[137], Hiroto Kishi[137], Tomoo Ishii[138], Masayuki Kanai[139], Tomonori Imamura[139], Tatsuya Yamashita[139], Masakiyo Yatomi[140], Toshitaka Maeno[140], Shinichi Hayashi[141], Mai Takahashi[141], Mizuki Kuramochi[141], Isamu Kamimaki[141], Yoshiteru Tominaga[141], Mitsuyoshi Utsugi[142], Akihiro Ono[142], Toru Tanaka[143], Takeru Kashiwada[143], Kazue Fujita[143], Yoshinobu Saito[143], Masahiro Seike[143], Masahiro Kanai[144], Ryunosuke Saiki[145], Takayoshi Hyugaji[146], Eigo Shimizu[146], KotoeKatayama[146], Satoru Miyawaki[147], Meiko Takahashi[148], Fumihiko Matsuda[148], Yosuke Omae[149], Yasuhito Nannya[145], Takafumi Ueno[150], Yukinori Okada[46,47,55,151], Ryuji Koike[152], Yuko Kitagawa[153], Katsushi Tokunaga[149], Akinori Kimura[154], Seiya Imoto[146], Satoru Miyano[23], Seishi Ogawa[145,155,156], Takanori Kanai[13], Koichi Fukunaga[1]

1. Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan.
2. Department of Infectious Diseases, Keio University School of Medicine, Tokyo, Japan.
3. Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

Otake *et al. BMC Infectious Diseases*   (2022) 22:735

Page 9 of 12

4. Department of General Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

5. Department of Emergency and Disaster Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

6. Department of Cardiovascular Biology and Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

7. Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

8. Department of Nephrology, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan.

9. Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan.

10. Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Tokyo, Japan

11. Department of Anesthesiology, Keio University School of Medicine, Tokyo, Japan.

12. Department of Laboratory Medicine, Keio University School of Medicine, Tokyo, Japan

13. Division of Gastroenterology and Hepatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan.

14. Keio University Health Center, Keio University School of Medicine, Tokyo, Japan.

15. Department of Organoid Medicine, Keio University School of Medicine, Tokyo, Japan.

16. Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan.

17. Department of Infection Control, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan.

18. JCHO (Japan Community Health Care Organization) Saitama Medical Center, Internal Medicine, Saitama, Japan.

19. Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan.

20. Department of Respiratory Medicine, Tokyo Women's Medical University, Tokyo, Japan.

21. Department of General Medicine, Tokyo Women's Medical University, Tokyo, Japan.

22. Department of Emergency and Critical Care Medicine, Kansai Medical University General Medical Center, Moriguchi, Japan.

23. M&D Data Science Center, Tokyo Medical and Dental University, Tokyo, Japan.

24. Clinical Research Center, Tokyo Medical and Dental University Hospital of Medicine, Tokyo, Japan.

25. Department of Medical Informatics, Tokyo Medical and Dental University Hospital of Medicine, Tokyo, Japan.

26. Respiratory Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

27. Clinical Laboratory, Tokyo Medical and Dental University Hospital of Medicine, Tokyo, Japan.

28. Department of Insured Medical Care Management, Tokyo Medical and Dental University Hospital of Medicine, Tokyo, Japan

29. Fukujuji Hospital, Kiyose, Japan.

30. Kawasaki Municipal Ida Hospital, Department of Internal Medicine, Kawasaki, Japan.

31. Department of Infectious Diseases, Tosei General Hospital, Seto, Japan.

32. Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan.

33. Department of Respiratory Medicine, Kitasato University Kitasato Institute Hospital, Tokyo, Japan.

34. School of Veterinary Medicine, Kitasato University, Towada, Japan.

35. Laboratory of Viral Infection I, Department of Infection Control and Immunology, Ōmura Satoshi Memorial Institute & Graduate School of Infection Control Sciences, Kitasato University, Tokyo, Japan.

36. Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

37. Department of Infectious Diseases, Tohoku University Graduate School of Medicine, Sendai, Japan

38. Saiseikai Utsunomiya Hospital, Utsunomiya, Japan.

39. Department of Pulmonary Medicine, Saitama City Hospital, Saitama, Japan.

40. Department of Infectious Diseases, Saitama City Hospital, Saitama, Japan.

41. Department of General Thoracic Surgery, Saitama City Hospital, Saitama, Japan.

42. Department of Pulmonary Medicine, Eiju General Hospital, Tokyo, Japan.

43. Division of Infection Control, Eiju General Hospital, Tokyo, Japan.

44. Department of Hematology, Eiju General Hospital, Tokyo, Japan.

45. Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Suita, Japan.

46. Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan.

47. Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Suita, Japan.

48. Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita, Japan.

49. Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan

50. Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Japan.

51. Division of Infection Control and Prevention, Osaka University Hospital, Suita, Japan.

52. Department of Biomedical Ethics and Public Policy, Osaka University Graduate School of Medicine, Suita, Japan.

53. Department of Otolaryngology and Head and Neck Surgery, Kansai Rosai Hospital, Hyogo, Japan

54. Department of Immunopathology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan.

55. The Center for Infectious Disease Education and Research (CiDER), Osaka University, Suita, Japan.

56. Department of Respiratory Medicine, Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Japan.

57. Department of Clinical Laboratory, Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Japan.

58. Internal Medicine, Internal Medicine Center, Showa University Koto Toyosu Hospital, Tokyo, Japan.

59. Internal Medicine, Sano Kosei General Hospital, Sano, Japan.

60. Ishikawa Prefectural Central Hospital, Kanazawa, Japan.

61. Tachikawa Hospital, Tachikawa, Japan.

62. Department of Emergency and Critical Care Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan.

63. Department of Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan.

64. Department of Pediatrics, Tokyo Women's Medical University Medical Center East, Tokyo, Japan.

65. Japan Community Health care Organization Kanazawa Hospital, Kanazawa, Japan.

66. Department of Respiratory Medicine, Japan Organization of Occupational Health and Safety, Kanto Rosai Hospital, Kawasaki, Japan.

67. Department of General Internal Medicine, Japan Organization of Occupational Health and Safety, Kanto Rosai Hospital, Kawasaki, Japan.

68. Sapporo City General Hospital, Sapporo, Japan.

69. Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

70. Department of Infection Control, Fukuoka University Hospital, Fukuoka, Japan.

71. Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan.

72. Department of Respiratory Medicine, National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

73. Department of Allergy, National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

74. Department of General Internal Medicine and Infectious Diseases, National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

75. Department of Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi, Japan.

76. Keiyu Hospital, Yokohama, Japan.

77. Division of Respiratory Medicine, Social Welfare Organization Saiseikai Imperial Gift Foundation, Inc., Saiseikai Kumamoto Hospital, Kumamoto, Japan.

78. KKR SapporoMedical Center, Department of respiratory medicine, Sapporo, Japan.

79. Division of General Internal Medicine, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan.

80. Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Kawasaki, Japan.

81. Japanese Red Cross Medical Center, Tokyo, Japan.

82. Matsumoto City Hospital, Matsumoto, Japan.

83. Department of Rheumatology, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan.

84. Department of Respiratory Medicine, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan.

85. Department of Emergency and Critical Care Medicine, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan.

86. NHO Kanazawa Medical Center, Kanazawa, Japan.

87. Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan.

88. Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.

89. Nihon University School of Medicine, Department of Internal Medicine, Division of Respiratory Medicine, Tokyo, Japan.

90. Musashino Red Cross Hospital, Musashino, Japan.

91. Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan.

92. Ome Municipal General Hospital, Ome, Japan.

93. Fukuoka Tokushukai Hospital, Department of Internal Medicine, Kasuga, Japan.

94. Fukuoka Tokushukai Hospital, Respiratory Medicine, Kasuga, Japan.

95. National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan.

96. Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Tokorozawa, Japan.

97. Division of Infectious Diseases and Respiratory Medicine, Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan.

98. Department of Respiratory Medicine, Fujisawa City Hospital, Fujisawa, Japan.

99. Department of Internal Medicine, Tokyo Saiseikai Central Hospital, Tokyo, Japan.

100. Department of Pulmonary Medicine, Tokyo Saiseikai Central Hospital, Tokyo, Japan.

101. Uji-Tokushukai Medical Center, Uji, Japan.

102. Department of Infectious Disease and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka Japan.

103. Department of Respirology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan.

104. Division of Respirology, Rheumatology, and Neurology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan.

105. Department of Infectious Disease, National Hospital Organization Kyushu Medical Center, Fukuoka Japan.

106. Department of Cardiology, Pulmonology, and Nephrology, Yamagata University Faculty of Medicine, Yamagata, Japan.

107. Department of Pulmonary Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

108. Department of Emergency and Critical Care Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

109. Department of Hematology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

110. Department of Nephrology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

111. Department of Cardiovascular Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

112. Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

113. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

114. Daini Osaka Police Hospital, Osaka, Japan.

115. Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine, Isehara, Japan.

116. Department of Anesthesiology and Intensive Care Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

117. Department of Infection Control and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

118. Department of Respiratory Internal Medicine, St. Marianna University School of Medicine, Yokohama-City Seibu Hospital, Yokohama, Japan.

119. Gifu University School of Medicine Graduate School of Medicine, Emergency and Disaster Medicine, Gifu, Japan.

120. KINSHUKAI Hanwa The Second Hospital, Osaka, Japan.

121. Department of Respiratory Medicine, Tokyo Medical University Hospital, Tokyo, Japan.

122. JA Toride medical hospital, Toride, Japan.

123. Okayama Rosai Hospital, Okayama, Japan.

124. Himeji St. Mary's Hospital, Himeji, Japan.

125. Emergency & Critical Care, Niigata University, Niigata, Japan.

126. Emergency & Critical Care Center, National Hospital Organization Kyoto Medical Center, Kyoto, Japan.

127. National Hospital Organization Tokyo National Hospital, Kiyose, Japan.

128. Fujioka General Hospital, Fujioka, Japan.

129. Department of General Medicine, School of Medicine, International University of Health and Welfare Shioya Hospital, Ohtawara Japan.

130. Department of Pharmacology, School of Pharmacy, International University of Health and Welfare Shioya Hospital, Ohtawara Japan.

131. Department of Respiratory Medicine, International University of Health and Welfare Shioya Hospital, Ohtawara Japan.

132. Department of Clinical Laboratory, International University of Health and Welfare Shioya Hospital, Ohtawara Japan.

133. Department of General Medicine, School of Medicine, International University of Health and Welfare, Narita Japan.

134. Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan.

135. Kansai Electric Power Hospital, Osaka, Japan.

136. Department of Infectious Diseases, Kumamoto City Hospital, Kumamoto, Japan.

137. Department of Respiratory Medicine, Kumamoto City Hospital, Kumamoto, Japan.

138. Tokyo Medical University Ibaraki Medical Center, Inashiki, Japan.

139. Department of Emergency and Critical Care Medicine, Tokyo Metropolitan Police Hospital, Tokyo, Japan.

140. Department of Respiratory Medicine, Gunma University Graduate School of Medicine, Maebashi, Japan.

141. National hospital organization Saitama Hospital, Wako, Japan.

142. Department of Internal Medicine, Kiryu Kosei General Hospital, Kiryu, Japan.

143. Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

144. Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.

145. Department of Pathology and Tumor Biology, Kyoto University, Kyoto, Japan.

146. Division of Health Medical Intelligence, Human Genome Center, the Institute of Medical Science, the University of Tokyo, Tokyo, Japan.

147. Department of Neurosurgery, Faculty of Medicine, the University of Tokyo, Tokyo, Japan.

148. Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

149. Genome Medical Science Project (Toyama), National Center for Global Health and Medicine, Tokyo, Japan.

150. Department of Biomolecular Engineering, Graduate School of Tokyo Institute of Technology, Tokyo, Japan.

151. Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan.

152. Medical Innovation Promotion Center, Tokyo Medical and Dental University, Tokyo, Japan.

153. Department of Surgery, Keio University School of Medicine, Tokyo, Japan.

154. Institute of Research, Tokyo Medical and Dental University, Tokyo, Japan.

155. Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Kyoto, Japan.

156. Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institute, Stockholm, Sweden.

Otake *et al. BMC Infectious Diseases*   (2022) 22:735

Page 11 of 12

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of Keio University School of Medicine (20200061) and related research institutions. All adult participants provided written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflicts of interest.

Author details
[1]Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, 35 Shinanomachi, Tokyo 160-8582, Japan. [2]Department of Infectious Diseases, Keio University School of Medicine, Tokyo, Japan. [3]Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan. [4]Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan. [5]JCHO (Japan Community Health Care Organization) Saitama Medical Center, Internal Medicine, Saitama, Japan. [6]Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan. [7]Department of Respiratory Medicine, Tokyo Women's Medical University, Tokyo, Japan. [8]Department of Emergency and Critical Care Medicine, Kansai Medical University General Medical Center, Moriguchi, Japan. [9]Department of Respiratory Medicine, Fukujuji Hospital, Kiyose, Japan. [10]Department of Internal Medicine, Kawasaki Municipal Ida Hospital, Kawasaki, Japan. [11]Department of Infectious Diseases, Tosei General Hospital, Seto, Japan. [12]Department of Respiratory Medicine, Kitasato University Kitasato Institute Hospital, Tokyo, Japan. [13]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan. [14]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan. [15]Medical Innovation Promotion Center, Tokyo Medical and Dental University, Tokyo, Japan. [16]Department of Surgery, Keio University School of Medicine, Tokyo, Japan. [17]Institute of Research, Tokyo Medical and Dental University, Tokyo, Japan. [18]Division of Health Medical Intelligence, Human Genome Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan. [19]M&D Data Science Center, Tokyo Medical and Dental University, Tokyo, Japan. [20]Department of Pathology and Tumor Biology, Kyoto University, Kyoto, Japan. [21]Division of Gastroenterology and Hepatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan.

References
1. Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, et al. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020;883:173375.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324:782–93.
3. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. J Chin Med Assoc. 2021;84(1):3–8.
4. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549–57.
5. Shankar-Hari M, Rubenfeld GD. Population enrichment for critical care trials: phenotypes and differential outcomes. Curr Opin Crit Care. 2019;25:489–97.
6. Rubio-Rivas M, Corbella X, Mora-Luján JM, Loureiro-Amigo J, López Sampalo A, Yera Bergua C, et al. Predicting clinical outcome with phenotypic clusters in COVID-19 pneumonia: an analysis of 12,066 hospitalized patients from the Spanish registry SEMI-COVID-19. J Clin Med. 2020;9:3488.
7. Ye W, Lu W, Tang Y, Chen G, Li X, Ji C, et al. Identification of COVID-19 clinical phenotypes by principal component analysis-based cluster analysis. Front Med (Lausanne). 2020;7:570614.
8. Lusczek ER, Ingraham NE, Karam BS, Proper J, Siegel L, Helgeson ES, et al. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. PLoS ONE. 2021;16:e0248956.
9. Dupont T, Caillat-Zucman S, Fremeaux-Bacchi V, Morin F, Lengliné E, Darmon M, et al. Identification of distinct immunophenotypes in critically ill coronavirus disease 2019 patients. Chest. 2021;159:1884–93.
10. Vasquez CR, Gupta S, Miano TA, Roche M, Hsu J, Yang W, et al. Identification of distinct clinical subphenotypes in critically ill patients with COVID-19. Chest. 2021;160:929–43.
11. Reddy K, Sinha P, O'Kane CM, Gordon AC, Calfee CS, McAuley DF. Subphenotypes in critical care: translation into clinical practice. Lancet Respir Med. 2020;8:631–43.
12. Ishii M, Terai H, Kabata H, Masaki K, Chubachi S, Tateno H, et al. Clinical characteristics of 345 patients with coronavirus disease 2019 in Japan: a multicenter retrospective study. J Infect. 2020;81:e3-5.
13. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–6.
14. Ministry of Health LaW, Situation report. https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html.
15. Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Asai Y, Tsuzuki S, et al. Clinical epidemiology of hospitalized patients with COVID-19 in Japan: report of the COVID-19 REGISTRY JAPAN. Clin Infect Dis. 2020;73:e3677–89.
16. Namkoong H. Japan COVID-19 Task Force: a nation-wide consortium to elucidate host genetics of COVID-19 pandemic in Japan. medRxiv. 2021.
17. Tanaka H, Namkoong H, Lee H, Morita A, Chubachi S, Kabata H, et al. Clinical characteristics of patients with coronavirus disease (COVID-19): preliminary baseline report of Japan COVID-19 task force, a nation-wide consortium to investigate host genetics of COVID-19. Int J Infect Dis. 2021;113:74–81.
18. World Health Organization. Novel coronavirus: COVID-19 therapeutic trial synopsis. February 18, novel coronavirus: COVID-19 therapeutic trial synopsis. 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.
19. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81:e16-25.
20. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev. 2021;37:e3377.
21. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110–8.
22. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14:303–10.
23. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335–7.
24. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol. 2020;92:1915–21.

25. Kovalic AJ, Satapathy SK, Thuluvath PJ. Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis. Hepatol Int. 2020;14:612–20.
26. McLachlan GJ. Cluster analysis and related techniques in medical research. Stat Methods Med Res. 1992;1:27–48.
27. Ye W, Robbins RT. Cluster analysis of longidorus species (nematoda: longidoridae), a new approach in species identification. J Nematol. 2004;36:207–19.
28. Foster KJ, Jauregui E, Tajudeen B, Bishehsari F, Mahdavinia M. Smell loss is a prognostic factor for lower severity of coronavirus disease 2019. Ann Allergy Asthma Immunol. 2020;125:481–3.
29. Porta-Etessam J, Núñez-Gil IJ, González García N, Fernandez-Perez C, Viana-Llamas MC, Eid CM, et al. COVID-19 anosmia and gustatory symptoms as a prognosis factor: a subanalysis of the HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) registry. Infection. 2021;49:677–84.
30. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med. 2020;180:1081–9.
31. Sobhani S, Aryan R, Kalantari E, Soltani S, Malek N, Pirzadeh P, et al. Association between clinical characteristics and laboratory findings with outcome of hospitalized COVID-19 patients: a report from Northeast Iran. Interdiscip Perspect Infect Dis. 2021;2021:5552138.
32. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020;7:e671–8.
33. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
34. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934–43.
35. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802–10.
36. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, Fotiou D, Migkou M, Tzanninis IG, et al. Emerging treatment strategies for COVID-19 infection. Clin Exp Med. 2021;21:167–79.
37. DeMerle K, Angus DC, Seymour CW. Precision medicine for COVID-19: phenotype anarchy or promise realized? JAMA. 2021;325:2041–2.
38. Chauhan K, Pattharanitima P, Piani F, Johnson RJ, Uribarri J, Chan L, et al. Prevalence and outcomes associated with hyperuricemia in hospitalized patients with COVID-19. Am J Nephrol. 2022;53:78–86.
39. Deniz C, Selçuk Y, Kubilay I, Ahmed CG, Didar S, Ahmed BG, et al. Uric acid and mortality relationship in covid-19. Acta Medica Mediterranea. 2022;38(1):725–31.
40. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol. 2013;25:210–6.
41. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep. 2018;8:4314.
42. Ripabelli G, Sammarco ML, Cannizzaro F, Montanaro C, Ponzio GV, Tamburro M. A coronavirus outbreak linked to a funeral among a Romani community in Central Italy. Front Med (Lausanne). 2021;8:617264.
43. Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50:e13362.
44. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020;44:1792–7.
45. Raman R, Patel KJ, Ranjan K. COVID-19: unmasking emerging SARS-CoV-2 variants, vaccines and therapeutic strategies. Biomolecules. 2021;11:993.

Publisher's Note