Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 122 (2022) 747–754

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

U-shaped association between abnormal serum uric acid levels and COVID-19 severity: reports from the Japan COVID-19 Task Force

Takahiro Fukushima[a], Shotaro Chubachi[a,*], Ho Namkoong[a], Shiro Otake[a], Kensuke Nakagawara[a], Hiromu Tanaka[a], Ho Lee[a], Atsuho Morita[a], Mayuko Watase[a], Tatsuya Kusumoto[a], Katsunori Masaki[a], Hirofumi Kamata[a], Makoto Ishii[a], Naoki Hasegawa[b], Norihiro Harada[c], Tetsuya Ueda[d], Soichiro Ueda[e], Takashi Ishiguro[f], Ken Arimura[g], Fukuki Saito[h], Takashi Yoshiyama[i], Yasushi Nakano[j], Yoshikazu Mutoh[k], Yusuke Suzuki[l], Koji Murakami[m], Yukinori Okada[n,o,p], Ryuji Koike[q], Yuko Kitagawa[r], Akinori Kimura[s], Seiya Imoto[t], Satoru Miyano[u], Seishi Ogawa[v,w], Takanori Kanai[x], Koichi Fukunaga[a], the Japan COVID-19 Task Force

[a] Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
[b] Department of Infectious Diseases, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
[c] Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan
[d] Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan
[e] JCHO (Japan Community Health Care Organization) Saitama Medical Center, Internal Medicine, Saitama, Japan
[f] Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan
[g] Department of Respiratory Medicine, Tokyo Women's Medical University, Tokyo, Japan
[h] Department of Emergency and Critical Care Medicine, Kansai Medical University General Medical Center, Moriguchi, Japan
[i] Department of Respiratory Medicine, Fukujuji hospital, Kiyose, Japan
[j] Department of Internal Medicine, Kawasaki Municipal Ida Hospital, Kawasaki, Japan
[k] Department of Infectious Diseases, Tosei General Hospital, Seto, Japan
[l] Department of Respiratory Medicine, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
[m] Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[n] Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan
[o] Department of Genome Informatics, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
[p] Laboratory for Systems Genetics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
[q] Medical Innovation Promotion Center, Tokyo Medical and Dental University, Tokyo, Japan
[r] Department of Surgery, Keio University School of Medicine, Tokyo, Japan
[s] Institute of Research, Tokyo Medical and Dental University, Tokyo, Japan
[t] Division of Health Medical Intelligence, Human Genome Center, the Institute of Medical Science, the University of Tokyo, Tokyo, Japan
[u] M&D Data Science Center, Tokyo Medical and Dental University, Tokyo, Japan
[v] Department of Pathology and Tumor Biology, Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Kyoto, Japan
[w] Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institute, Stockholm, Sweden
[x] Division of Gastroenterology and Hepatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 20 January 2022
Revised 28 May 2022
Accepted 4 July 2022

ABSTRACT

Objectives: This study aimed to identify the relationship between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity in the Japanese population.
Methods: We included 1523 patients enrolled in the Japan COVID-19 Task Force cohort between February 2020 and May 2021. We compared the clinical characteristics, including co-morbidities, laboratory findings, and outcomes, particularly invasive mechanical ventilation (IMV), among patients with and without abnormal uric acid levels or a history of hyperuricemia.
Results: Patients with high serum uric acid levels were older and had higher body weight and body mass index than those without. In addition, the multiple logistic regression analysis revealed a significant association between high serum uric acid levels or a history of hyperuricemia and an increased risk of

* Corresponding author: Shotaro Chubachi, Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine. 35 Shinanomachi, Tokyo 160-8582, Japan, Telephone: 03-5363-3793; Fax: 03-3353-2502
E-mail address: bachibachi472000@live.jp (S. Chubachi).

https://doi.org/10.1016/j.ijid.2022.07.014

Keywords:
COVID-19
Hyperuricemia
Hypouricemia
High serum uric acid
Low serum uric acid
Respiratory care
Severity

IMV (odds ratio [OR] = 1.77; $P = 0.03$/OR = 1.56; $P = 0.04$). Moreover, patients with low uric acid levels on admission were also associated significantly with the requirement of IMV (OR = 5.09; $P < 0.0001$).
Conclusion: Abnormal serum uric acid levels or a history of hyperuricemia were significantly associated with COVID-19 severity in the Japanese cohort.

Introduction

COVID-19 is caused by SARS-CoV-2 and is a worldwide pandemic. Until October 2021, there were more than 235 million confirmed COVID-19 cases and over 4.5 million confirmed deaths worldwide (Our World in Data, 2021). The pandemic is still not displaying any signs of ending, making it difficult to deliver routine medical care. Limited medical resources warrant determining ways to provide appropriate treatment to individuals prone to this disease. Therefore, it is essential to understand the risk factors for severe COVID-19.

The risk factors for increasing COVID-19 severity include patient characteristics such as male gender (Grasselli et al., 2020), obesity (Popkin et al., 2020), and age (O'Driscoll et al., 2021) in addition to co-morbidities such as hypertension (Pranata et al., 2020), chronic lung disease (Nishiga et al., 2020), and type 2 diabetes (Holman et al., 2020). Despite few reports on an association between a history of hyperuricemia and COVID-19 severity, a small retrospective study found that a history of hyperuricemia was associated with an increased COVID-19 mortality rate (Ishii et al., 2020).

Hyperuricemia increases the risk of hypertension (Fei et al., 2008) and cardiovascular disease (Cannon et al., 1966; Tuttle et al., 2001). The prevalence of hyperuricemia varies among countries (Wallace et al., 2004). In Japan, over 10 million patients present hyperuricemia. Approximately 30% of men in their 30s and 40s and 25% of those in their 50s and 60s suffer from hyperuricemia; thus, it is a common condition that can also affect younger individuals (Japan Preventive Association of Life-style related Disease, 2021). A history of hyperuricemia and abnormal serum uric acid levels are associated with several types of lifestyle-related diseases and have been hypothesized to be associated with COVID-19 severity (Ghazanfari et al., 2021; Ishii et al., 2020; Zheng et al., 2021).

Previous reports have described an association between high serum uric acid levels and COVID-19 severity, particularly mortality or the rate of using invasive mechanical ventilation (IMV) (Ghazanfari et al., 2021; Zheng et al., 2021). However, researchers have also reported an association between low serum uric acid levels and COVID-19 severity (Dufour et al., 2021; Werion et al., 2020). Some studies have shown a U-shaped association between serum uric acid levels and the risk of death (Cho et al., 2018; Hu et al., 2020). Therefore, a similar association between serum uric acid levels and COVID-19 severity may exist. However, the precise relationship between COVID-19 severity and serum uric acid levels is unknown.

In this study, we aimed to identify the relationship between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity in a large Japanese cohort.

Methods

Study design and Settings

The study design and setting have been previously described (Tanaka et al., 2021). All COVID-19 cases in this retrospective cohort study were recruited through the Japan COVID-19 Task Force. From February 2020 to May 2021, data were collected from consecutive inpatients aged ≥18 years and diagnosed with COVID-19, using the SARS-CoV-2 polymerase chain reaction results at one of the affiliated hospitals (>100). The data of patients who agreed to participate in the study were registered in an electronic case record form. Patients meeting any of the following criteria were excluded: (i) non-Japanese; (ii) with incomplete medical records, such as the inability to obtain the use of IMV or no data regarding the serum uric acid levels. Among the 1976 patients who met the inclusion criteria, we excluded 51 non-Japanese patients. In addition, 379 patients with no data on serum uric acid levels and 23 patients with unknown IMV use were excluded. Thus, 1523 patients were included in the analysis (Fig. 1a).

Written or oral informed consent was obtained from all patients. This study was approved by the ethics committees of the 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 the World Medical Association General Assembly, Fortaleza, Brazil, in October 2013.

Data collection and definitions

We extracted the following information from the electronic case record forms: age, sex, body weight, body mass index (BMI), smoking history, clinical symptoms and signs, co-morbidities, laboratory findings on admission, and disease severity (required IMV). All laboratory tests were performed according to the clinical care needs. The symptoms and signs were included during referral and admission as well as during hospitalization. The laboratory results were collected within 48 hours of the initial visit or admission. Individual clinicians determined co-morbidities such as a history of hyperuricemia and chronic kidney disease by conducting interviews with each patient or evaluating the electronic medical records. The recorded data were reviewed by a team of respiratory clinicians. For missing core data, the first clinician to diagnose the disease was contacted to collect it. Missing or absent data in the patient background were noted as unknown.

Statistical analysis

Continuous and categorical variables are presented as means or percentages, respectively. The data were compared between the groups with and without a history of hyperuricemia using the *t*-test and χ^2 test, as appropriate. To investigate the relationship between serum uric acid levels or a history of hyperuricemia and IMV use, we performed a multivariable logistic regression analysis to adjust for previously analyzed factors (Hendren et al., 2021; Ishii et al., 2020). The models were adjusted for age and chronic kidney disease (model 1), or in addition for sex, a history of hypertension, diabetes mellitus, chronic lung disease, and cardiovascular disease (model 2). We presented the adjusted odds ratio (OR) with a 95% confidence interval (95% CI). Statistical significance was set at $P < 0.05$. All data were analyzed using the JMP 16 program (SAS Institute Japan Ltd., Tokyo, Japan).

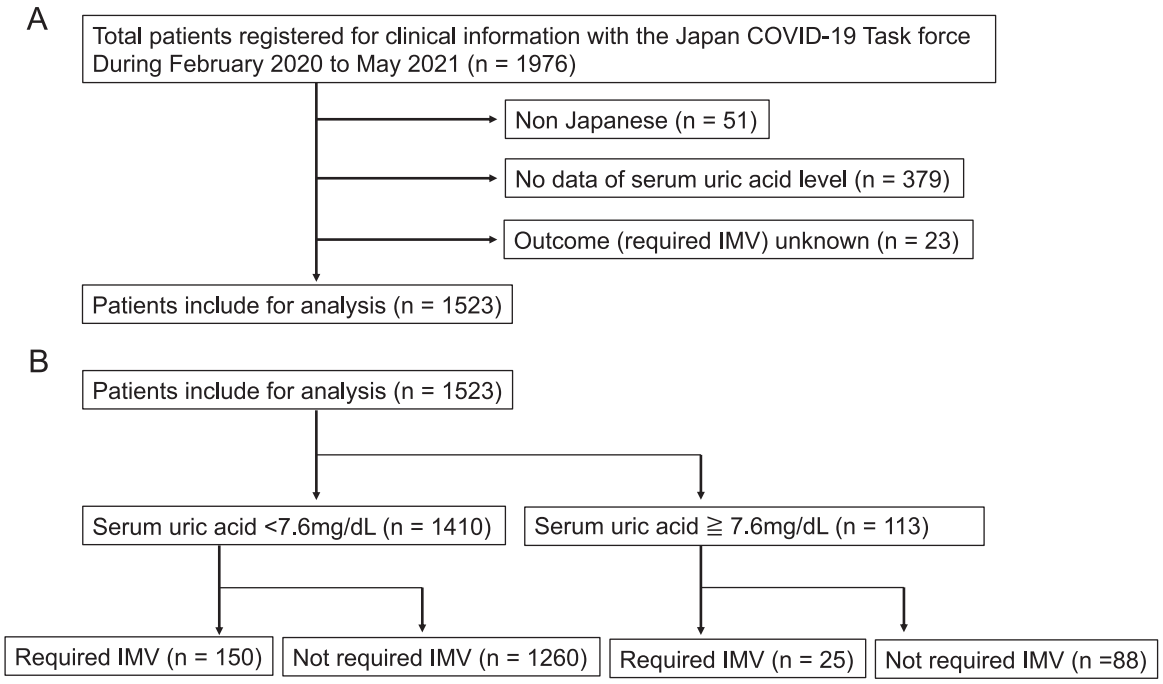

Fig. 1. Consort diagram of patient selection. a. Overall, 1976 patients with COVID-19 were registered during the study period, and 1523 patients were included in the analysis. b. The study included 1523 patients and was stratified by optimal cut-off for baseline serum uric acid levels (<7.6 mg/dl or ≧7.6 mg/dl)

Results

Comparison of baseline characteristics between patients with and without high serum uric acid levels on admission

On the 1523 patients included in this study, we performed a univariate logistic analysis to investigate the optimal cut-off value for the serum uric acid levels to predict the requirement of IMV. Receiver operating characteristic curves demonstrated that the optimal cut-off for baseline serum uric acid levels for predicting IMV requirement was 7.6 mg/dl (area under the curve [AUC] 0.49; $P = 0.04$). The distribution of serum uric acid levels among the 1523 patients is shown in Supplemental Figure 1. A total of 113 patients had serum uric acid levels ≧7.6 mg/dl. Among them, 25 patients (22.1%) required IMV (Fig. 1b). Table 1 lists the baseline characteristics of patients according to the baseline serum uric acid levels. Compared with patients with serum uric acid levels <7.6 mg/dl, those with serum uric acid levels ≧7.6 mg/dl were more likely to be older ($P = 0.002$) and had a higher body weight ($P = 0.002$) and BMI ($P = 0.005$). There was no significant difference in the rate of each sign and symptom on admission, except for disturbance of consciousness ($P < 0.0001$) and sore throat ($P = 0.01$) between the groups. Hypertension, cardiovascular disease, and chronic kidney disease were observed in 58 (51.8%), 19 (16.8%), and 29 (26.4%) patients with serum uric acid levels ≧7.6 mg/dl, respectively, all with a statistically significant prevalence ($P < 0.05$). A history of hyperuricemia was also significantly more common in patients with serum uric acid levels ≧7.6 mg/dl ($P = 0.01$). The laboratory findings revealed higher white blood cells, c-reactive protein (CRP), and ferritin levels among patients with serum uric acid levels ≧7.6 mg/dl; with high blood urea nitrogen, creatinine, lactate dehydrogenase, potassium, brain natriuretic peptide, HbA1c, and procalcitonin. Patients with serum uric acid levels ≧7.6 mg/dl also demonstrated a higher rate of bacterial infection than those without ($P = 0.003$).

Association between serum uric acid levels and required IMV

The rate of required IMV was significantly higher in patients with serum uric acid levels ≧7.6 mg/dl than in those with levels <7.6 mg/dl ($P = 0.0002$) (Fig. 2a). After an adjustment for the age and chronic kidney disease diagnosis in model 1, serum uric acid levels ≧7.6 mg/dl were independently associated with the requirement of IMV in the multiple logistic regression analysis (OR = 1.77 [1.07-2.93]; $P = 0.03$) (Fig. 2b). The rate of death was also significantly higher in patients with serum uric acid levels ≧7.6 mg/dl ($P < 0.0001$) (Fig. 3a). Patients with serum uric acid levels ≧7.6 mg/dl were also found to have an independent association with death (OR = 2.72 [1.34-5.50]; $P = 0.005$) (Fig. 3b). The rate of oxygen required on admission was significantly higher in these patients ($P = 0.0002$) and was found to have a significant association on the multiple logistic regression analysis (OR = 1.74 [1.08-2.78]; $P = 0.02$) (Fig. 4). In addition, among 969 patients who did not require oxygen on admission, those with serum uric acid levels ≧7.6 mg/dl were also associated with an increased risk of requiring IMV after admission ($P = 0.009$). However, among 284 patients who required oxygen on admission, high serum uric acid levels were not associated with an increased risk of requiring IMV after admission ($P = 0.50$).

After adjustment for age, sex, history of chronic kidney disease, hypertension, diabetes mellitus, chronic lung disease, and cardiovascular disease in model 2, serum uric acid levels ≧7.6 mg/dl were associated with the following outcomes in the multiple logistic regression analysis (required IMV: OR = 1.84 [1.09-3.09]; $P = 0.02$; death: OR = 2.49 [1.19-5.19]; $P = 0.02$; required oxygen: OR = 1.72 [1.06-2.80]; $P = 0.03$). Using a serum uric acid cut-off value of >7.0 mg/dl, which is the definition of hyperuricemia in Japan, the rate of required IMV was significantly increased (n = 26; 16.7%, $P = 0.03$). However, a serum uric acid level >7.0 mg/dl was not significantly associated with IMV in the multivariable analysis (OR = 1.28, $P = 0.32$).

Table 1
A comparison of the characteristics between the patients with uric acid levels <7.6 mg/dl and ≧7.6 mg/dl on admission.

Parameters	All patients N = 1523	UA <7.6 mg/dl n = 1410	UA ≧7.6 mg/dl n = 113	*P*-value[a]
Age in years, mean (95% CI)	59.3 (58.4-60.1)	58.9 (57.9-59.8)	63.9 (60.7-67.2)	0.002
Sex, n (%)				
Male	1023 (67.2)	939 (66.6)	84 (74.34)	
Female	500 (32.8)	471 (33.4)	29 (25.7)	0.09
Body weight, median (95% CI)	67.0 (66.1-67.8)	66.6 (65.7-67.5)	71.8 (68.6-75.0)	0.002
BMI, median (95% CI)	24.6 (24.4-24.9)	24.5 (24.2-24.8)	25.9 (25.0-26.9)	0.005
Smoking history				
Current smoker, n (%)	222 (15.3)	199 (14.8)	23 (21.7)	0.08
Ex-smoker, n (%)	666 (46.3)	609 (45.8)	57 (53.3)	0.19
Brinkman index, median (95% CI)	671.6 (602.2-741.0)	676.9 (604.2-749.6)	616.1 (380.1-852.0)	0.77
Signs and symptoms, n (%)				
Disturbance of consciousness	56 (3.7)	44 (3.2)	12 (10.7)	<0.0001
Fever	1182 (78.3)	1095 (78.4)	87 (77.7)	0.85
Cough	862 (57.4)	805 (57.8)	57 (51.8)	0.22
Sputum	356 (23.7)	328 (23.6)	28 (25.2)	0.7
Sore throat	346 (23.1)	331 (24.0)	15 (13.3)	0.01
Nasal discharge	227 (15.2)	216 (15.6)	11 (9.8)	0.1
Dysgeusia	267 (17.8)	254 (18.3)	13 (11.5)	0.07
Dysosmia	245 (16.4)	232 (16.8)	13 (11.5)	0.23
Dyspnea	475 (32.1)	432 (31.6)	43 (39.1)	0.1
Malaise	736 (49.0)	676 (48.7)	60 (53.1)	0.37
Co-morbidities, n (%)				
Hyperuricemia	177 (11.8)	156 (11.2)	21 (19.1)	0.01
Hypertension	560 (37.3)	502 (36.2)	58 (51.8)	0.001
Diabetes mellitus	355 (23.5)	321 (22.9)	34 (30.6)	0.07
Cardiovascular disease	164 (10.8)	145 (10.4)	19 (16.8)	0.03
Chronic lung disease	76 (5.1)	66 (4.7)	10 (9.1)	0.04
Chronic kidney disease	130 (9.0)	101 (7.6)	29 (26.4)	<0.0001
Laboratory findings, median (95% CI)				
WBC ($\times 10^3$/dl)	5.8 (5.7-6.0)	5.8 (5.6-6.0)	6.5 (5.9-7.0)	0.02
Neutrocyte (fraction, %)	69.9 (69.2-70.6)	69.8 (69.1-70.5)	71.2 (68.8-73.8)	0.27
Lymphocyte (fraction, %)	21.6 (21.0-22.3)	21.8 (21.2-22.5)	19.2 (16.8-21.5)	0.03
Eosinocyte (fraction, %)	0.87 (0.77-0.98)	0.87 (0.76-0.98)	0.89 (0.51-1.28)	0.91
Hemoglobin (g/dl)	14.0 (13.9-14.1)	14.0 (13.9-14.1)	13.6 (13.3-14.0)	0.04
Platelet ($\times 10^4$/dl)	19.8 (19.4-20.1)	19.9 (19.5-20.3)	18.5 (17.2-19.8)	0.05
Albumin (g/dl)	3.7 (3.6-3.7)	3.7 (3.7-3.8)	3.5 (3.4-3.6)	0.0003
T-Bil (mg/dl)	0.68 (0.66-0.70)	0.68 (0.66-0.70)	0.63 (0.56-0.71)	0.23
γGTP (U/l)	66.5 (62.0-70.9)	66.3 (61.7-71.9)	68.5 (52.1-85.0)	0.8
AST (U/l)	42.0 (38.4-45.7)	40.9 (37.1-44.7)	56.3 (43.0-69.6)	0.03
ALT (U/l)	40.0 (35.1-44.7)	39.4(34.4-44.3)	46.5 (29.1-64.0)	0.44
BUN (mg/dl)	17.8 (17.1-18.6)	16.6 (15.9-17.4)	32.4 (29.8-35.1)	<0.0001
Creatinine (mg/dl)	1.15 (1.07-1.23)	1.04 (0.96-1.13)	2.5 (2.23-2.82)	<0.0001
LDH (U/l)	276 (270-283)	272 (265-278)	330 (307-354)	<0.0001
Uric acid (mg/dl)	4.9 (4.8-5.0)	4.6 (4.5-4.6)	9.2 (8.9-9.4)	<0.0001
CK (U/l)	158 (134-183)	150 (124-175)	257 (167-346)	0.02
Na (mEq/l)	138.3 (138.1-138.5)	138.3 (138.1-138.5)	138.3 (137.6-139.0)	0.95
K (mEq/l)	3.99 (3.97-4.02)	3.98 (3.96-4.00)	4.14 (4.05-4.23)	0.0003
Cl* (mEq/l)	101.9 (101.7-102.1)	101.9 (101.7-102.1)	101.6 (100.9-102.4)	0.51
BNP (pg/ml)	73.0 (45.9-100.0)	62.8 (34.9-90.8)	206.8 (105.1-308.4)	0.008
Ferritin (ng/ml)	560 (526-594)	549 (514-584)	703 (573-833)	0.03
HbA1c (%)	6.4 (6.3-6.5)	6.4 (6.3-6.4)	6.7 (6.4-6.9)	0.04
D-dimer (ng/ml)	2.5 (2.0-2.9)	2.2 (1.8-2.7)	5.2 (3.7-6.7)	0.0002
Procalcitonin (ng/ml)	0.28 (0.20-0.35)	0.25 (0.17-0.32)	0.68 (0.41-0.94)	0.003
CRP (mg/dl)	4.9 (4.6-5.2)	4.8 (4.5-5.1)	5.9 (4.9-7.0)	0.04
Complication of bacterial infection, n (%)	187 (12.4)	163 (11.6)	24 (21.2)	0.003
Required oxygen therapy, n (%)	284 (22.7)	247 (21.4)	37 (38.1)	0.0002

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; CI, confidence interval; Cl*, chloride; CRP, C-reactive protein; K, kalium; LDH, lactate dehydrogenase; Na, natrium; UA, uric acid; WBC, white blood cell.

[a] The *P*-values compared the data between the patients with and without hyperuricemia during hospitalization using the Pearson's chi-square test.

Subsequently, we evaluated the association between the serum uric acid levels defined by various cut-off levels and the requirement of IMV using multivariable logistic regression analysis in model 1 (Fig. 5). Patients with uric acid levels >8.5 mg/dl, 8.0 mg/dl, or 7.5 mg/dl were significantly associated with the requirement of IMV (OR = 2.97 [1.59-5.56], 1.97 [1.14-3.42], and 1.77 [1.07-2.93]). In contrast, those with low uric acid levels <2.0 mg/dl, <2.5 mg/dl, or 3.0 mg/dl were also significantly associated with the requirement of IMV (OR = 5.09 [2.43-10.64], 3.00 [1.69-5.32], 1.70 [1.06-2.70]). Likewise, after adjustment in model 2, these serum uric acid levels were associated with the requirement of IMV (<2.0 mg/dl; OR = 5.29 [2.36-11.85]; *P* <0.0001, <2.5 mg/dl; OR = 3.48 [1.87-6.47]; *P* <0.0001, <3.0 mg/dl; OR = 1.98 [1.20-3.28]; *P* = 0.008, >8.0 mg/dl; OR = 1.99 [1.13-3.51]; *P* = 0.02, >8.5 mg/dl; OR = 2.99 [1.57-5.71]; *P* = 0.0009).

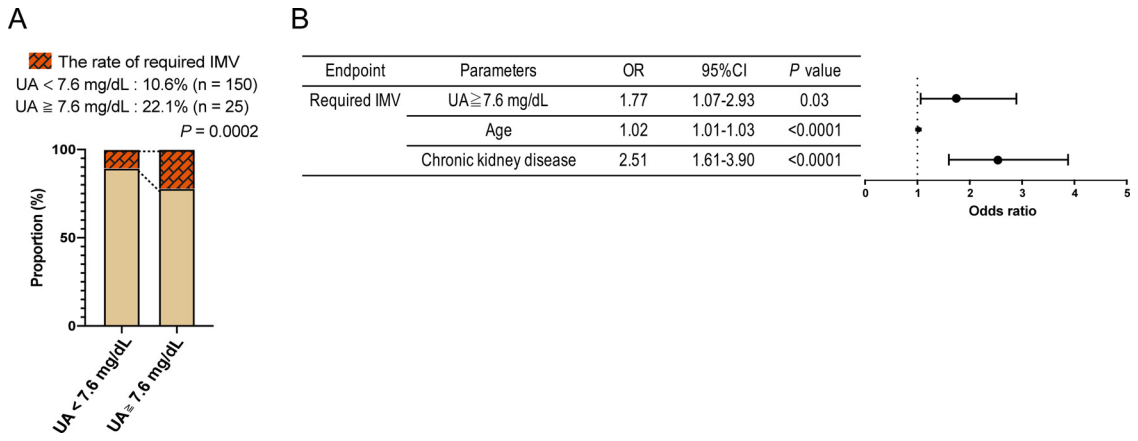

Fig. 2. The relationship between patients with COVID-19 and high serum uric acid levels on admission and their outcomes (required IMV). a. The proportion of requirement of IMV in patients with and without high serum uric acid levels on admission. b. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and required IMV. IMV, invasive mechanical ventilation.

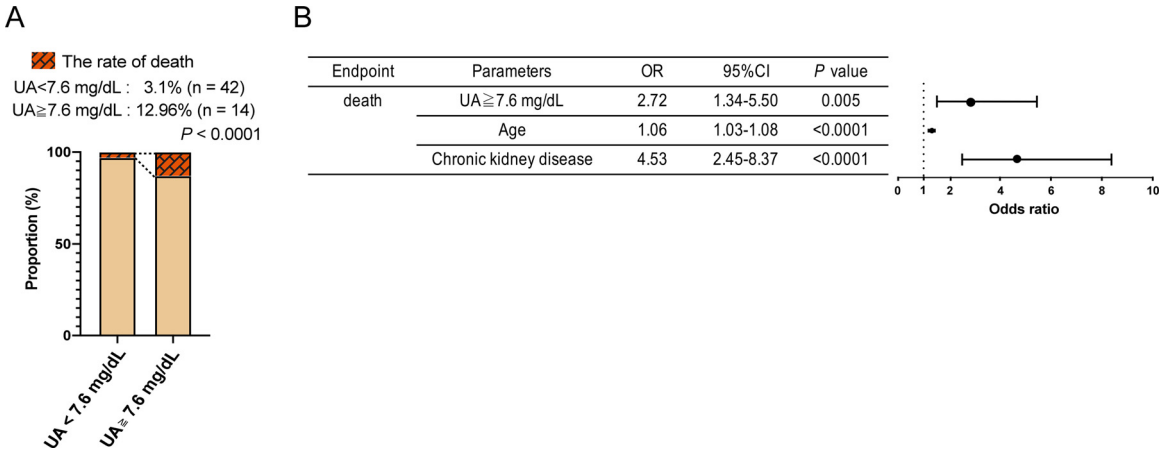

Fig. 3. The relationship between patients with COVID-19 and high serum uric acid levels on admission and their outcomes (death). a. The proportion of death in patients with and without high serum uric acid levels on admission. b. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and death.

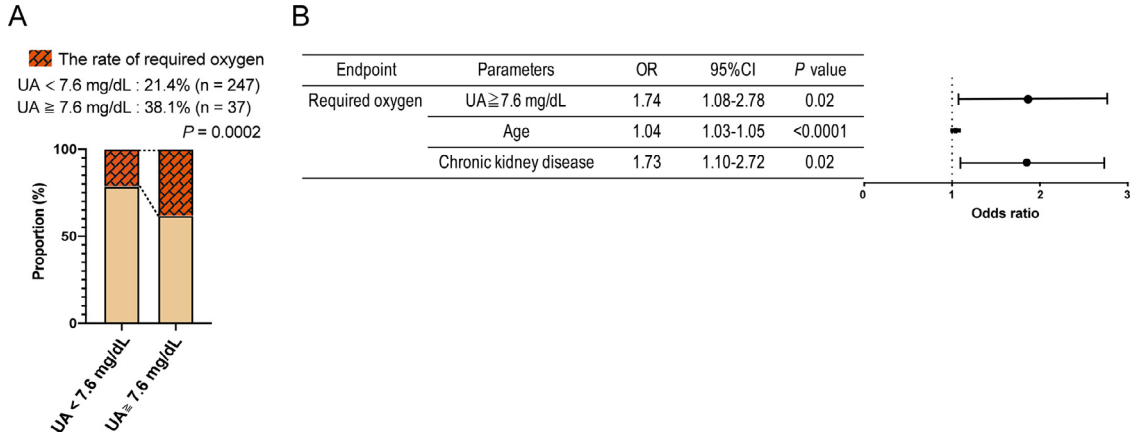

Fig. 4. The relationship between patients with COVID-19 and high serum uric acid levels on admission and required oxygen. a. The proportion of required oxygen in patients with and without high serum uric acid levels on admission.. b. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and oxygen requirement.

Comparison of baseline characteristics between patients with and without a history of hyperuricemia

Patients with a history of hyperuricemia were more likely to be men (P <0.0001), older (P = 0.001), and had a higher body weight (P <0.0001) and BMI (P <0.0001) (Supplemental Table 1). Moreover, they demonstrated significantly higher rates of hypertension (P <0.0001), diabetes mellitus (P = 0.0003), cardiovascular disease (P <0.0001), and chronic kidney disease (P <0.0001). The laboratory findings demonstrated substantially higher ferritin (P <0.0001) and CRP (P = 0.04) in these patients.

Endpoint	Parameters	OR	95%CI	*P* value
Required IMV	UA<2.0 mg/dL	5.09	2.43-10.64	<0.0001
	UA<2.5 mg/dL	3.00	1.69-5.32	0.0002
	UA<3.0 mg/dL	1.70	1.06-2.70	0.02
	UA<3.5 mg/dL	1.36	0.93-2.00	0.11
	UA<4.5 mg/dL	1.29	0.92-1.79	0.14
	UA<5.5 mg/dL	0.99	0.70-1.41	0.98
	UA<6.5 mg/dL	0.94	0.61-1.43	0.76
	UA>7.0 mg/dL	1.28	0.79-2.06	0.32
	UA>7.5 mg/dL	1.77	1.07-2.93	0.03
	UA>8.0 mg/dL	1.97	1.14-3.42	0.02
	UA>8.5 mg/dL	2.97	1.59-5.56	0.0007

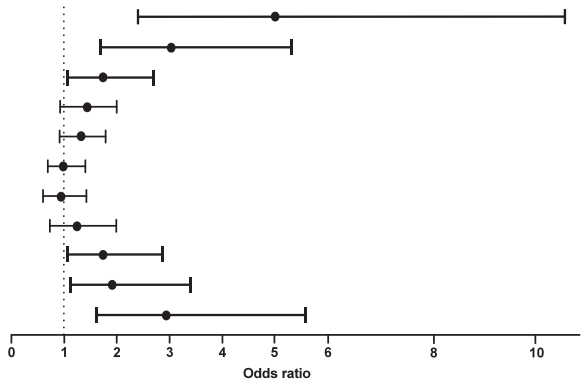

Fig. 5. Multivariable logistic regression analysis for IMV use by serum uric acid levels IMV, invasive mechanical ventilation.

The rate of required IMV was significantly higher in patients with a history of hyperuricemia than in those without ($P = 0.002$) (Supplemental Figure 2a). A history of hyperuricemia was independently associated with the requirement of IMV in the multiple logistic regression analysis following only model 1 (OR = 1.56 [95% CI: 1.01-2.43]; $P = 0.04$) (Supplemental Figure 2b).

Discussion

This is the first study to our knowledge to report the relationship between uric acid levels and COVID-19 severity in a Japanese cohort. Furthermore, we first indicated that abnormal serum uric acid levels on admission and a history of hyperuricemia are associated with the requirement of IMV. Our findings could help us predict the need for intubation and optimize patient allocation for special therapies. Previous reports have described an association between low serum uric acid levels (Dufour et al., 2021; Liu et al., 2021; Li et al., 2021; Werion et al., 2020), high uric acid (Ghazanfari et al., 2021; Zheng et al., 2021), and COVID-19 severity. In this study, high uric acid levels were associated with COVID-19 severity in terms of co-morbidity; similarly, low uric acid levels were independently associated with COVID-19 severity. The Japanese definition of hyperuricemia (serum uric acid levels >7.0 mg/dl) (Japan Preventive Association of Life-style related Disease, 2021) was not significant; however, a high uric acid level greater than the cut-off value of 7.6 mg/dl could predict the severity. In contrast, the Japanese definition of hypouricemia (serum uric acid levels <2.0 mg/dl) (Kuwabara et al., 2017) and low serum acid level greater than the cut-off value of 2.5 mg/dl could predict the severity. Both low and high uric acid levels were associated with COVID-19 severity outcomes, suggesting that the association between uric acid levels and COVID-19 severity may be mediated by more than one different pathogenic mechanism.

Uric acid is a product of purine metabolism, and the serum uric acid level reflects the counterbalance between uric acid production and excretion. Serum uric acid level increases because of tissue damage. In the event of tissue damage, uric acid stored intracellularly is released from the cells, causing hyperuricemia (Ghazanfari et al., 2021; Zheng et al., 2021). Severe COVID-19 causes multiple pathophysiological effects, including oxidative stress, inflammation, endothelial dysfunction, renin-angiotensin-aldosterone system activation, and insulin resistance (Govender et al., 2021; Montiel et al., 2022; Vaduganathan et al., 2020). Our study revealed that the high inflammatory state might reflect tissue damage in patients with high serum uric acid levels on admission, and it may progress to more severe outcomes after admission. This is supported by the result that patients with high serum uric acid levels already had a high rate of required oxygen upon admission. This inference could be made because of a Japanese cohort that was hospitalized based on background disease and other risk factors even in the absence of oxygen requirement. Therefore, high serum uric acid levels on admission may act as a direct biomarker of COVID-19 severity.

Meanwhile, patients with high uric acid levels on admission demonstrated several baseline characteristics previously associated with COVID-19 severity. First, these patients were older (O'Driscoll et al., 2021), smokers (Shastri et al., 2021; World Health Organization, 2021), and obese (Zheng et al., 2020). Second, their co-morbidities included hypertension (Bailly et al., 2021), diabetes mellitus (Ando et al., 2021; Fried et al., 2021), cardiovascular disease (Nishiga et al., 2020), and chronic kidney disease (Cheng et al., 2020; Genovesi et al., 2021; Petrilli et al., 2020; Sullivan et al., 2022; Williamson et al., 2020). In addition, poor prognostic laboratory biomarkers were higher in these patients (D-dimer) (Xu et al., 2020), CRP (Brasen et al., 2021), and ferritin (Deng et al., 2021)). These may reflect a complex interaction of uric acid levels and COVID-19 severity. The previously mentioned co-morbidities may be confounding factors in the association between the history of hyperuricemia and the requirement for IMV in patients with COVID-19. However, after adjusting for these risk factors, abnormal serum uric acid levels were independently associated with IMV. Likewise, patients with a history of hyperuricemia also demonstrated similar baseline characteristics, and this was found to be independently associated with the requirement of IMV after adjusting for age and chronic kidney disease. However, the history of hyperuricemia was not an independent factor in model 2, which included multiple co-morbidities, presumably because of the confounding effect with other co-morbidities or the effect of the lowering of the uric acid levels by a hyperuricemia drug. Therefore, from our study, patients with high uric acid levels on admission or a history of hyperuricemia can be assumed to have an independent factor predicting COVID-19 severity. We previously reported on the relationship between hyperuricemia-related genes and COVID-19 severity in a large genome-wide association study (Namkoong et al., 2021). Thus, genetic predisposition to hyperuricemia is also supposedly related to COVID-19 severity, which supports the results of our study.

Interestingly, our findings demonstrated that low serum uric acid levels on admission were also associated significantly with IMV requirement. The AUC of the receiver operating curve for baseline serum uric acid levels was relatively low. This was because not only high serum uric acid levels but also low serum uric acid levels were associated with IMV use. Low serum uric acid levels may directly reflect COVID-19 severity through renal tubular dysfunction. Previously, a clinical and autopsy study reported evidence for proximal tubule dysfunction in a subset of patients with COVID-19,

with low-molecular-weight proteinuria, neutral aminoaciduria, and defective handling of uric acid or phosphate (Dufour et al., 2021; Werion et al., 2020). The previously mentioned studies confirmed the relationship between low serum uric acid levels and COVID-19 severity, such as the rate of IMV use and death. Serum uric acid levels are lowest 2-3 weeks after hospitalization and subsequently increase (Liu et al., 2021). Therefore, low serum uric acid levels are also a possible biomarker reflecting COVID-19 severity through renal dysfunction, particularly proximal tubule dysfunction.

This study had some limitations. First, we extracted the history of hyperuricemia and chronic kidney disease by conducting interviews with each patient or evaluating the medical records. The criteria for extraction of the history of hyperuricemia or chronic kidney disease may have differed among individual institutions. Only 10% of patients had a history of hyperuricemia in this study, which is less than the prevalence of hyperuricemia in the Japanese population (20-30%) (Japan Preventive Association of Life-style related Disease, 2021). It may have resulted in a lower prevalence than the actual prevalence. The same is assumed regarding the history of chronic kidney disease. Thus, undiagnosed chronic kidney disease could be a confounding factor in the association between a history of hyperuricemia and COVID-19 severity. In addition, we did not record regular patient medications, and it was impossible to determine whether hyperuricemia was being currently treated, treated previously, or only recorded. We speculate that in patients with abnormal serum uric acid levels, the regular use of hypouricemia drugs may be effective in preventing the severity of COVID-19. This warrants further studies evaluating the effectiveness of hyperuricemia treatment for COVID-19. Second, the duration between the onset of the disease and the collection of serum uric acid levels was unclear. Blood samples were collected during hospitalization within 48 hours.

Moreover, serum uric acid levels vary among patients with COVID-19. One study reported that low serum uric acid levels last for only 4 days and subsequently increase (Dufour et al., 2021) contrary to others. We did not examine the changes in serum uric acid levels after hospitalization, which made the interpretation difficult. This necessitates further studies to address the aforementioned limitations in the future.

Conclusion

In a large Japanese cohort study, we evaluated the correlation between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity. Our findings indicated an association between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity, such as IMV use, suggesting a prognostic role in patients with COVID-19. More studies are required to evaluate the complex associations between abnormal serum uric acid and COVID-19 severity.

Funding source

This study was supported by AMED (JP20nk0101612, JP20fk0108415, JP21jk0210034, JP21km0405211, and JP21km0405217), JST CREST (JPMJCR20H2), MHLW (20CA2054), Takeda Science Foundation, Mitsubishi Foundation, and Bioinformatics Initiative of Osaka University Graduate School of Medicine, Osaka University.

Ethical approval

This study was approved by the ethics committee of the Keio University School of Medicine (20200061) and affiliated institutes.

Authors contributions

Conceptualization: TF, SC, HN, KM, HK, MI, NH, and KF.
Data curation: TF, KN, HT, HL, AM, SO, MW, and TK.
Formal analysis: TF, SC.
Methodology: TF, SC, and HN.
Supervision: SC, NH, KM, HK, MI, NH, NH, TU, SU, TI, KA, FS, TY, YN, YM, YS, KM, YO, RK, YK, AK, SI, SM, SO, TK, and KF.
Visualization: SC, HN.
Writing - original draft: TF, SC.
Writing - review and editing: TF, SC, NH, KM, HK, MI, NH, NH, TU, SU, TI, KA, FS, TY, YN, YM, YS, KM, YO, RK, YK, AK, SI, SM, SO, TK, and KF.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgments

We would like to thank all participants involved in this study and all members of the Japan COVID-19 Task Force who regularly engaged in clinical and research work on COVID-19. All members contributed to this study. Supplemental files named “Author information” summarizes the members who contributed to the collection and analysis of cases at each institution.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.014.

References

Ando W, Horii T, Uematsu T, Hanaki H, Atsuda K, Otori K. Impact of overlapping risks of type 2 diabetes and obesity on coronavirus disease severity in the United States. Sci Rep 2021;11:17968.
Brasen CL, Christensen H, Olsen DA, Kahns S, Andersen RF, Madsen JB, Lassen A, Kierkegaard H, Jensen A, Sydenham TV, Madsen JS, Møller JK, Brandslund I. Daily monitoring of viral load measured as SARS-CoV-2 antigen and RNA in blood, IL-6, CRP and complement C3d predicts outcome in patients hospitalized with COVID-19. Clin Chem Lab Med 2021;59:1988–97.
Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl J Med 1966;275:457–64.
Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829–38.
Cho SK, Chang Y, Kim I, Ryu S. U-shaped association between serum uric acid level and risk of mortality: a cohort study. Arthritis Rheumatol 2018;70:1122–32.
Deng F, Zhang L, Lyu L, Lu Z, Gao D, Ma X, Guo Y, Wang R, Gong S, Jiang W. Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. Med Clin (Engl Ed) 2021;156:324–31.
Dufour I, Werion A, Belkhir L, Wisniewska A, Perrot M, De Greef J, Schmit G, Yombi JC, Wittebole X, Laterre PF, Jadoul M, Gérard L, Morelle J. CUSL COVID-19 Research Group. Serum uric acid, disease severity and outcomes in COVID-19. Crit Care 2021;25:212.
Namkoong H, Edahiro R, Fukunaga K, Shirai Y, Sonehara K, Tanaka H, et al. Japan COVID-19 Task Force: a nation-wide consortium to elucidate host genetics of COVID-19 pandemic in Japan. medRxiv 2021. https://www.medrxiv.org/content/10.1101/2021.05.17.21256513v1 (accessed on 14th July 2022)
Bailly L, Fabre R, Courjon J, Carles M, Dellamonica J, Pradier C. Obesity, diabetes, hypertension and severe outcomes among inpatients with coronavirus disease 2019: a nationwide study. Clin Microbiol Infect 2021;28:114–23.
Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–21.
Fried MW, Crawford JM, Mospan AR, Watkins SE, Munoz B, Zink RC, Elliott S, Burleson K, Landis C, Reddy KR, Brown RS. Patient characteristics and outcomes of 11 721 patients with coronavirus disease 2019 (COVID-19) hospitalized across the United States. Clin Infect Dis 2021;72:e558–65.
Genovesi S, Rebora P, Occhino G, Rossi E, Maloberti A, Belli M, Bonfanti P, Giannattasio C, Rossetti C, Epis OM, Ughi N, Valsecchi MG. Atrial fibrillation and clinical outcomes in a cohort of hospitalized patients with SARS-CoV-2 infection and chronic kidney disease. J Clin Med 2021;10:4108.
Ghazanfari T, Salehi MR, Namaki S, Arabkheradmand J, Rostamian A, Rajabnia Chenary M, Ghaffarpour S, Kaboudanian Ardestani S, Edalatifard M, Naghizadeh MM, Mohammadi S, Mahloujirad M, Izadi A, Ghanaati H, Beigmohammadi MT, Vodjgani M, Mohammad Shirazi B, Mirsharif ES, Abdollahi A,

Mohammadi M, Emadi Kouchak H, Dehghan Manshadi SA, Zamani MS, Mahmoodi Aliabadi M, Jamali D, Khajavirad N, Mohseni Majd AM, Nasiri Z, Faghihzadeh S. Interpretation of hematological, biochemical, and immunological findings of COVID-19 disease: biomarkers associated with severity and mortality. Iran J Allergy Asthma Immunol 2021;20:46–66.

Govender N, Khaliq OP, Moodley J, Naicker T. Insulin resistance in COVID-19 and diabetes. Prim Care Diabetes 2021;15:629–34.

Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, Laffey J, Carrafiello G, Carsana L, Rizzuto C, Zanella A, Scaravilli V, Pizzilli G, Grieco DL, Di Meglio L, de Pascale G, Lanza E, Monteduro F, Zompatori M, Filippini C, Locatelli F, Cecconi M, Fumagalli R, Nava S, Vincent JL, Antonelli M, Slutsky AS, Pesenti A, Ranieri VM. collaborators. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8:1201–8.

Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation 2021;143:135–44.

Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020;8:823–33.

Hu L, Hu G, Xu BP, Zhu L, Zhou W, Wang T, Bao H, Cheng X. U-shaped association of serum uric acid with all-cause and cause-specific mortality in US Adults: a cohort study. J Clin Endocrinol Metab 2020;105 dgz068.

Ishii M, Terai H, Kabata H, Masaki K, Chubachi S, Tateno H, Nakamura M, Nishio K, Koh H, Watanabe R, Ueda S, Terashima T, Suzuki Y, Yagi K, Miyao N, Minematsu N, Inoue T, Nakachi I, Namkoong H, Okamori S, Ikemura S, Kamata H, Yasuda H, Kawada I, Hasegawa N, Fukunaga K. Keio COVID-19 Research Consortium (K-CORC) and the Keio Donner Project Team. Clinical characteristics of 345 patients with coronavirus disease 2019 in Japan: a multicenter retrospective study. J Infect 2020;81:e3–5.

Japan Preventive Association of Life-style related Disease. Survey and statistics of lifestyle-related diseases, http://www.seikatsusyukanbyo.com/statistics/disease/hyperuricemia/; 2022 (accessed 07 January 2022).

Kuwabara M, Niwa K, Ohtahara A, Hamada T, Miyazaki S, Mizuta E, Ogino K, Hisatome I. Prevalence and complications of hypouricemia in a general population: a large-scale cross-sectional study in Japan. PLoS One 2017;12.

Li G, Wu X, Zhou CL, Wang YM, Song B, Cheng XB, Dong QF, Wang LL, You SS, Ba YM. Uric acid as a prognostic factor and critical marker of COVID-19. Sci Rep 2021;11:17791.

Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 2020;21.

Liu YM, Xie J, Chen MM, Zhang X, Cheng X, Li H, Zhou F, Qin JJ, Lei F, Chen Z, Lin L, Yang C, Mao W, Chen G, Lu H, Xia X, Wang D, Liao X, Yang J, Huang X, Zhang BH, Yuan Y, Cai J, Zhang XJ, Wang Y, Zhang X, She ZG, Li H. Kidney Function Indicators Predict Adverse Outcomes of COVID-19. Med (N Y) 2021;2:38–48 e2.

Montiel V, Lobysheva I, Gérard L, Vermeersch M, Perez-Morga D, Castelein T, et al. Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients. EBioMedicine 2022;77.

Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17:543–58.

O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, Fontanet A, Cauchemez S, Salje H. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 2021;590:140–5.

Our World in Data. Coronavirus pandemic (COVID-19)– the data. https://ourworldindata.org/coronavirus-data, 2021 (accessed 07 January 2021).

Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, Alsukait RF, Alluhidan M, Alazemi N, Shekar M. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev 2020;21:e13128.

Shastri MD, Shukla SD, Chong WC, Kc R, Dua K, Patel RP, Peterson GM, O'Toole RF. Smoking and COVID-19: what we know so far. Respir Med 2021;176.

Sullivan MK, Lees JS, Drake TM, Docherty AB. Oates G, Hardwick HE, Russell CD, Merson L, Dunning J, Nguyen-Van-Tam JS, Openshaw P, Harrison EM, Baillie JK, ISARIC4C Investigators, Semple MG, Ho A, Mark PB. Acute kidney injury in patients hospitalized with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. Nephrol Dial Transplant 2022;37:271–84.

Tanaka H, Lee H, Morita A, Namkoong H, Chubachi S, Kabata H, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Murakami K, Okada Y, Koike R, Kitagawa Y, Tokunaga K, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K. Japan COVID-19 Task Force. Clinical characteristics of patients with coronavirus disease (COVID-19): preliminary baseline report of Japan COVID-19 Task Force, a nationwide consortium to investigate host genetics of COVID-19. Int J Infect Dis 2021;113:74–81.

Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. Am J Cardiol 2001;87:1411–14.

Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9.

Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 2004;31:1582–7.

Werion A, Belkhir L, Perrot M, Schmit G, Aydin S, Chen Z, et al. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. Kidney Int 2020;98:1296–307.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.

World Health Organization. WHO statement: tobacco use and COVID-19. https://www.who.int/news/item/11-05-2020-who-statement-tobacco-use-and-covid-19, 2021 (accessed 07 January 2021).

Xu Y, Qian Y, Gu Q, Tang J. Relationship between D-dimer concentration and inflammatory factors or organ function in patients with coronavirus disease 2019. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2020;32:559–63.

Zheng KI, Gao F, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, Liu WY, George J, Zheng MH. Letter to the Editor: obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism 2020;108.

Zheng T, Liu X, Wei Y, Li X, Zheng B, Gong Q, Dong L, Zhong J. Laboratory predictors of COVID-19 mortality: a retrospective analysis from Tongji Hospital in Wuhan. Mediators Inflamm 2021;2021.