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.

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Letter to the Editor

Clinical characteristics of 345 patients with coronavirus disease 2019 in Japan: A multicenter retrospective study

Lu and colleagues recently reviewed mortality-related risk factors of COVID-19.[1] COVID-19 was first reported in Wuhan, China, in December 2019 and subsequently spread globally, leading to a pandemic;[2] as of August 25, 2020, more than 23 million people worldwide had been confirmed to have COVID-19 infections, and more than 810,000 patients had died.[3] Although approximately 80% of COVID-19 cases are classified as mild or asymptomatic, 15% of adults infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) developed severe illness and required oxygen supplementation, and an additional 5% progressed to a critical state.[2]

An increasing number of literature indicated the specific risk factors for the progression of severe illness and poor outcomes resulting from COVID-19.[1] For example, a recent large-scale study demonstrated that older age and certain clinical conditions (diabetes, respiratory diseases, and heart, kidney, and autoimmune conditions) are risk factors for death from COVID-19.[4] Although there is a limited number of effective therapies to date, the identification of risk factors for disease progression and clinical outcomes is crucial, because it means appropriate care and the proper allocation of medical resources can be timely provided.

Japan is characterized by a rapidly aging population, with the highest proportion (28.4%) of elderly citizens (65 years and older) worldwide.[5] In Japan, the first case of COVID-19 was reported in mid-January 2020. The first outbreak in Japan occurred on the *Diamond Princess* cruise ship in February 2020. Since then, the number of COVID-19 patients has increased exponentially. A state of emergency was declared in Tokyo on April 7 and was subsequently lifted on May 25, 2020, due to the decreased number of newly diagnosed COVID-19 cases. Subsequently, the number of COVID-19 cases quickly increased again; more than 63,000 people had been diagnosed with COVID-19, and more than 1200 people had died of COVID-19 in Japan as of August 25, 2020.[3] A few studies have shown the clinical features or the risk factors for the progression of severe illness and death, in a large number of COVID-19 patients in Japan affected by community transmission, other than the *Diamond Princess* cruise ship.[6–8]

For this retrospective multicenter study, we evaluated the characteristics and prognostic factors of 345 patients with COVID-19, who were admitted to either Keio University Hospital or one of 13 community hospitals located in the Greater Tokyo Area from February 1 to June 19, 2020, to investigate the similarity in these risk factors to those previously reported in an aging country such as Japan. All patients were followed up until June 19, 2020 in the hospital or were discharged before June 19.

The median age of these patients was 54 years; 198 (57.4%) of the patients were male, and 327 (94.8%) were Japanese (Table 1). Additionally, 167 (48%) had at least one comorbidity, and 17 (6.1%) were obese (defined as a BMI (body mass index) of $\geq$30 kg/m^2). Among various comorbidities, hypertension was the most common (26.1%), followed by diabetes (13.9%) and hyperuricemia (8.1%). The median duration of illness before diagnosis was 5 days. The most common symptoms reported during the observation period were fever (3.0%), followed by cough (48.3%), which were consistent with previous report.[2]

Next, we compared the severe (those who required oxygen supplementation) and non-severe patient groups as well as the living and deceased groups. The number of patients with COVID-19 who required oxygen supplementation was 112 (32.5%), and the number of patients who died in the hospital was 23 (6.7%) (Table 1).

The risk factors that increased the need for oxygen supplementation were older age, male sex, history of smoking, various comorbidities (hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease [COPD], hyperuricemia, and chronic kidney disease), and specific disease symptoms (consciousness disorder, fever, shortness of breath, nausea/vomiting, and general fatigue) (Table 1).

Table 1 shows the positive risk factors for COVID-19-related death. We performed univariate analysis of risk factors for severe illness in patients with COVID-19 (not shown). Older age, male sex, a history of smoking, comorbidities (hypertension, diabetes, cardiovascular disease, COPD, hyperuricemia, and chronic kidney disease), and specific disease symptoms (consciousness disorder, fever, shortness of breath, nausea/vomiting, and general fatigue) were positively associated with the need for oxygen supplementation. Subsequently, we performed multivariate analysis of risk factors affecting the need for oxygen supplementation in COVID-19 patients (Table 2). Factors, including COPD (odds ratio [OR] 19.13), consciousness disorder (OR 9.23), shortness of breath (OR 4.74), and general fatigue (OR 3.74), were independently associated with the need for oxygen therapy in COVID-19 patients.

Univariate analysis of risk factors for death resulting from COVID-19 was performed (not shown). Older age, comorbidities (diabetes, cardiovascular disease, COPD, hyperuricemia, chronic liver disease, and chronic kidney disease), and specific symptoms (consciousness disorder and shortness of breath) were associated with death resulting from COVID-19. We further performed multivariate analysis of risk factors for death associated with SARS-CoV-2 infection (Table 2), and factors, including chronic kidney disease (OR 5.74), older age (OR 5.43), and hyperuricemia (OR 3.60), were independently associated with death resulting from COVID-19.

Our results demonstrate that chronic kidney disease (CKD), followed by older age and hyperuricemia, are the most common independent risk factors for COVID-19-related death in this study (Table 2). CKD and older age have been previously reported as risk factors for in-hospital death;[4] this is consistent with our data. However, preexisting hyperuricemia has not been previously re-

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Table 1
Clinical characteristics of 345 patients based on the severity of SARS-CoV-2 infection.

	Total	Severity at the end of observation		*p*-value	Outcomes		*p*-value
		non-severe	severe		alive at the end of observation	died in hospital	
N	345	233 (67.5%)	112 (32.5%)		322 (93.3%)	23 (6.7%)	
Age, median (IQR), y	54 (32–68)	41 (28–58)	67 (56–79)	<0.0001	52 (31.25–63)	80 (72.5–85)	<0.0001
0–17	13	13	0		13	0	
18–29	59	57	2		59	0	
30–49	82	67	15		81	1	
50–69	110	67	43		107	3	
70–89	72	26	46		57	15	
90-	9	3	6		5	4	
Sex							
Female	147 (42.6%)	112 (76.2%)	35 (23.8%)	0.0031	139 (94.6%)	8 (5.4%)	0.516
Male	198 (57.4%)	121 (61.1%)	77 (38.9%)		183 (92.4%)	15 (7.6%)	
Current or former smoker	117 (38.0%)	61 (52.1%)	56 (47.9%)	<0.0001	107 (91.5%)	10 (8.5%)	0.2523
Commodities							
Any	167 (48.4%)	81 (48.5%)	86 (51.5%)	<0.0001	146 (87.4%)	21 (12.6%)	< 0.0001
Hypertension	90 (26.1%)	34 (37.8%)	56 (62.2%)	<0.0001	80 (88.9%)	10 (11,1%)	0.0493
Diabetes	48 (13.9%)	21 (43.7%)	27 (56.3%)	0.0001	39 (81.3%)	9 (18.8%)	0.0003
Cardiovascular disease	23 (6.7%)	6 (26.1%)	17 (73.9%)	<0.0001	17 (73.9%)	6 (26.1%)	0.0001
Active malignant disease	27 (7.8%)	17 (63.0%)	10 (37.0%)	0.5971	23 (85.2%)	4 (14.8%)	0.0771
Immune-related disease	9 (2.6%)	4 (44.4%)	5 (55.6%)	0.1338	7 (77.8%)	2 (22.2%)	0.058
Chronic obstructive pulmonary disease	15 (4.3%)	1 (6.7%)	14 (93.3%)	<0.0001	11 (73.3%)	4 (26.7%)	0.0015
Bronchial asthma	22 (6.4%)	14 (63.6%)	8 (36.4%)	0.6864	22 (100%)	0 (0%)	0.1951
Hyperuricemia	28 (8.1%)	10 (35.7%)	18 (64.3%)	0.0002	21 (75.0%)	7 (25.0%)	<0.0001
Chronic liver disease	14 (4.1%)	7 (50.0%)	7 (50.0%)	0.1525	11 (78.6%)	3 (21.4%)	0.0238
Chronic kidney disease	17 (4.9%)	4 (23.5%)	13 (76.5%)	<0.0001	10 (58.8%)	7 (41.2%)	<0.0001
Symptoms reported							
Consciousness disorder	15 (4.3%)	3 (20.0%)	12 (80.0%)	<0.0001	10 (66.7%)	5 (33.3%)	<0.0001
Fever	252 (73.0%)	151 (59.9%)	101 (40.1%)	<0.0001	233 (92.5%)	19 (7.5%)	0.2846
Cough	166 (48.3%)	109 (65.7%)	57 (34.3%)	0.4278	156 (94.0%)	10 (6.0%)	0.635
Sputum	71 (20.6%)	43 (60.6%)	28 (39.4%)	0.1469	66 (93.0%)	5 (7.0%)	0.8927
Sore throat	61 (18.2%)	48 (88.7%)	13 (21.3%)	0.0341	60 (98.4%)	1 (1.6%)	0.0858
Rhinorrhoea	36 (10.5%)	35 (97.2%)	1 (2.8%)	<0.0001	36 (100%)	0 (0%)	0.0969
Taste disorder	69 (21.2%)	56 (81.2%)	13 (18.8%)	0.0068	69 (100%)	0 (0%)	0.0141
Olfactory disorder	55 (16.9%)	47 (85.5%)	8 (14.5%)	0.0011	55 (100%)	0 (0%)	0.0328
Shortness of breath	95 (28.0%)	39 (41.1%)	56 (58.9%)	<0.0001	84 (88.4%)	11 (11.6%)	0.0285
Diarrhea	46 (13.3%)	28 (60.9%)	18 (39.1%)	0.2996	42 (91.3%)	4 (8.7%)	0.5535
Nausea, vomiting	16 (4.7%)	7 (43.7%)	9 (56.3%)	0.0392	14 (87.5%)	2 (12.5%)	0.3494
General fatigue	133 (39.5%)	70 (52.6%)	63 (47.4%)	<0.0001	123 (92.5%)	10 (7.5%)	0.6834

Data are expressed as N (%) or median (interquartile range [IQR]). Data were analyzed by $\chi 2$ test or by Mann-Whitney U test where appropriate.

Table 2
Impact of risk factors for patients requiring oxygen therapy and after SARS-CoV-2 infection.

Risk factors (Oxygen therapy requirement)	Odds ratio (95% CI)	*p*-value*
Age group	2.24 (1.47–3.43)	< 0.001
Hypertension	3.34 (1.54–7.23)	0.006
Chronic obstructive pulmonary disease	19.13 (2.14–170.76)	0.008
Consciousness disorder	9.23 (1.52–56.18)	0.016
Rhinorrhoea	0.05 (0.01–0.44)	0.008
Shortness of breath	4.74 (2.31–9.73)	<0.001
General fatigue	3.74 (1.84–7.59)	<0.001
Risk factors (death)	**Odds ratio (95%CI)**	***p*-value***
Age group	5.43 (2.68–11.01)	<0.001
Hyperuricemia	3.60 (1.07–12.09)	0.038
Chronic kidney disease	5.74 (1.56–21.07)	0.009

* Mulitivariate logistic regression analysis was performed.
95% CI; 95% confidence interval.

ported as a risk factor for death resulting from COVID-19; to our knowledge, this is the first study demonstrating that hyperuricemia is an independent risk factor for death in COVID-19 patients. Hyperuricemia is a well-established risk factor for diabetes and CKD;[9] however, the mechanism underlying the relationship between hyperuricemia and COVID-19-related mortality is unclear. As inflammation and oxidative stress (key status in COVID-19 patients) have been reported as potential causes of higher mortality risks associated with hyperuricemia,[10] the inflammation and oxidative stress induced by SARS-CoV-2 infections likely contributed to this process.

In conclusion, we have shown the real-world clinical characteristics and risk factors for COVID-19 in the Greater Tokyo Area. Hyperuricemia is a novel risk factor for COVID-related death.

Declaration of Competing Interest

None.

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