Clinical Rheumatology (2022) 41:3661–3673
https://doi.org/10.1007/s10067-022-06305-w

ORIGINAL ARTICLE

Clinical characteristics of COVID-19 patients with underlying rheumatic diseases in Japan: data from a multicenter observational study using the COVID-19 Global Rheumatology Alliance physician-reported registry

Mari Kihara[1,2] · Takahiko Sugihara[3] · Junichi Asano[4,5] · Midori Sato[6] · Hiroshi Kaneko[7] · Sei Muraoka[8] · Shiro Ohshima[9] · Toshihiro Nanki[10]

Received: 19 May 2022 / Revised: 12 July 2022 / Accepted: 14 July 2022 / Published online: 16 August 2022

Abstract

Introduction To describe clinical characteristics of patients in Japan with coronavirus disease 19 (COVID-19) and pre-existing rheumatic disease and examine the possible risk factors associated with severe COVID-19.

Methods Adults with rheumatic disease and a COVID-19 diagnosis who were registered in the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry from Japan between 15 May 2020 and 12 May 2021 were included. Multivariable logistic regression models were used to assess factors associated with severe COVID-19 progression, defined as death or requiring oxygen inhalation.

Results In total, 222 patients were included in the study. Rheumatoid arthritis (48.2%), gout (14.4%), and systemic lupus erythematosus (8.1%) were the most common types of rheumatic disease, 55.1% of patients were in remission and 66.2% had comorbid disease. Most patients were hospitalised (86.9%) for COVID-19, 43.3% received oxygen, and 9.0% died. Older age (≥ 65 years), corticosteroid use, comorbid diabetes, and lung diseases are associated with higher risk for severe COVID-19 progression (odds ratio (OR) 3.52 [95% confidence interval (CI) 1.69–7.33], OR 2.68 [95% CI 1.23–5.83], OR 3.56 [95% CI 1.42–8.88], and OR 2.59 [95% CI 1.10–6.09], respectively).

Conclusions This study described clinical characteristics of COVID-19 patients with rheumatic diseases in Japan. Several possible risk factors for severe COVID-19 progression were suggested.

Key Points

- *Clinical characteristics of 222 adult patients in Japan with coronavirus disease 19 (COVID-19) and pre-existing rheumatic diseases were described.*
- *Most patients were hospitalised (86.9%) for COVID-19 in Japan, 43.3% received oxygen, and 9.0% died.*
- *The COVID-19 characteristics of patients with rheumatic diseases did not show any obvious different pattern from those of the general population in Japan.*
- *In this study, older age (≥ 65 years), corticosteroid use, comorbid diabetes, and lung diseases are associated with higher risk for severe COVID-19 progression.*

Keywords Antirheumatic agents · Coronavirus disease 2019 · Rheumatic diseases · Risk factors · Observational

Introduction

Severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) has spread rapidly since December 2019, resulting in the coronavirus disease 19 (COVID-19) global pandemic with significant morbidity and mortality [1]. Patients with chronic health conditions such rheumatic diseases, where they may be receiving

✉ Mari Kihara
kihara.rheu@tmd.ac.jp

Extended author information available on the last page of the article

immunosuppressive therapy, may be more vulnerable to infection and developing a more severe form of COVID-19. However, the current evidence is not clear, and the European Alliance of Associations for Rheumatology (EULAR) has advised that there is no evidence to support that patients with rheumatic musculoskeletal diseases have a higher risk of contracting SARS-CoV-2 or that they have a worse prognosis with COVID-19 [2–5]. On the other hand, it has been reported that SARS-CoV-2 infection leads to a hypersensitive response of the immune system in the later stage of COVID-19, which might lead to death or a severe outcome. Besides corticosteroids, antirheumatics such as IL-6 inhibitors and Janus kinase (JAK) inhibitors are recommended as treatment options for severe COVID-19 [6, 7].

In March 2020, the COVID-19 Global Rheumatology Alliance (C19-GRA) was formed to rapidly collect and disseminate information about the course of COVID-19 in patients with rheumatic disease and those being administered immunosuppressive medications [8–10]. Initial findings from the C19-GRA registry using data mainly from the USA and Europe highlighted several factors that were associated with an increased risk of hospitalisation, including older age, presence of comorbidities, and higher glucocorticoid dosage (≥ 10 mg/day of prednisolone equivalent) [11–13].

In Japan, the number of COVID-19 cases and deaths per population has been relatively low compared with Western countries [14], despite the fact that Japan has one of the most aged populations [15] and a high population density. The reasons for this are unclear, and information specific to the rheumatology population in Japan is currently unknown. Given the current absence of information regarding the course of COVID-19 in patients with rheumatic diseases in Japan, we conducted this study to describe the clinical characteristics of rheumatic disease patients with a diagnosis of COVID-19 in Japan and examine the possible risk factors associated with progression to severe COVID-19, defined as death or requiring oxygen inhalation.

Methods

Study design and patients: This was a retrospective, multicentre, observational study that used data from the C19-GRA physician-reported registry. In total, 79 hospitals and 19 clinics in Japan joined this study as a grass-root movement, and upon experiencing COVID-19 cases with underlying rheumatic diseases, they consequently registered all cases into this registry. A COVID-19 diagnosis was based on either polymerase chain reaction testing, antibody status, metagenomic testing, computed tomography scans, laboratory assays, or symptoms only [16].

The C19-GRA physician-reported registry was launched on 24 March 2020 and has been reported previously [8–10, 17]. In brief, registry data was collected voluntarily through a survey available to clinicians on the registry website (https://rheum-covid.org/). No patient identifiers, such as name or date of birth, were collected, and only de-identified information was captured by the survey. The data collected on case report forms included patient demographics, rheumatic disease phenotypes, physician-reported disease activities, comorbidities, usage of immunosuppressants and other drug therapies, COVID-19 phenotypes, treatments, and outcomes [8–10, 17].

A total of 222 adults who were residing in Japan registered in the C19-GRA physician-reported registry between 15 May 2020 and 12 May 2021 (diagnosed with COVID-19 between 1 January 2020 and 31 December 2020) were included in this study. Due to limited number of death cases, the primary outcome of interest was progression to severe COVID-19. Using the WHO severity definition, a low oxygen saturation (< 90% on room air) or severe respiratory distress [18], severe COVID-19 was defined as oxygen inhalation or death in this study. Oxygen status nor survival was not known for 13 cases, and these were excluded from the outcome analysis.

Ethical approval: The C19-GRA physician-reported registry was approved by the University of California, San Francisco Institutional Review Board as exempt research based on qualification as quality improvement/surveillance research, and not 'human subjects research'. This observational study of data for patients from Japan in the C19-GRA physician-reported registry was approved by the Ethics Committee of Toho University Omori medical centre (M20137 20,041 20,018).

Data analysis: Frequency (number and percentage [%]) was calculated for categorical variables, and summary statistics (median and interquartile range [IQR] or mean and standard deviation (SD)) were calculated for continuous data. The background factors of patients who progressed to severe COVID-19 versus those who did not were compared and *P* values were calculated using the Wilcoxon rank-sum test (for continuous variables) or chi-squared test (for categorical variables). Data were considered statistically significant for *P* values < 0.05. The odds ratios (OR) for both progression to severe disease and death as an outcome were analysed using a univariate logistic regression model and were reported alongside the corresponding 95% confidence intervals (CIs). For the multivariable logistic regression model for which progression to severe disease was an outcome, covariates included in the model were age, sex, and background factors with significant differences in the univariate analysis (with regards to complications, each were included separately), and risk factors identified in former studies [13, 19, 20]. For the multivariable logistic regression

model for which death was an outcome, sex, age, and rheumatic disease classification or type of therapeutic agent for rheumatic diseases were included as variables. STATA version 16 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

Results

Patients

A total of 222 adult patients in Japan with rheumatic disease and COVID-19 that was diagnosed between 1 January 2020 and 31 December 2020 were registered in the C19-GRA physician-reported registry between 15 May 2020 and 12 May 2021. Baseline demographic and clinical characteristics of these 222 patients are summarised in Table 1. The mean (SD) patient age was 63 (62.7 ± 14.6) years, 44.6% (99/222) were male, and 98.7% (219/222) were East Asian. Majority of cases (80.2% [166/207]) were from Kanto region. Of the 189 patients with available data on smoking history, 44.4% (84/189) were current or ex-smokers. The most common types of rheumatic disease in this population were rheumatoid arthritis (48.2% [107/222]), gout (14.4% [32/222]), and systemic lupus erythematosus (8.1% [18/222]). Most patients were reported to be in remission (55.1% [114/207]), although a low, moderate, or high level of disease activity was reported in 35.8% (74/207), 6.8% (14/207), and 2.4% (5/207) of patients, respectively (Table 1). The majority of patients had a comorbid disease (66.2% [147/222]). Key comorbidities included hypertension (32.9% [73/222]), diabetes mellitus (22.5% [50/222]), and a spectrum of lung diseases (23.0% [51/222]), including COPD/asthma (11.7% [26/222]) and intestinal lung disease (10.8% [24/222]) (Table 1).

Treatments for underlying rheumatic diseases

At the time of COVID-19 diagnosis, the treatments that patients were receiving for rheumatic disease included corticosteroids (45.5% [100/220]), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (44.1% [98/222]), biologic disease-modifying antirheumatic drugs (bDMARDs) (15.3% [34/222]), and JAK inhibitors (1.4% [3/222]) (Table 2). Most patients who were receiving bDMARDs or JAK inhibitors discontinued treatment after the onset of COVID-19 (81.8% [27/33], 100% [3/3], respectively) (Table 2).

COVID-19 characteristics and outcomes

Regarding the infection acquisition, 47.3% (105/222) of patients had a community-acquired infection of route unknown, 48.2% (107/222) of patients reported it was from a close contact, either at home or in the workplace, and 7.7% (17/222) of patients reported as healthcare-associated infection (Table 3). The most common diagnosis method was by polymerase chain reaction (91.9% [204/222]). CT was used for 18.9% [42/222] of patients. The common disease symptoms were fever (88.2% [165/187]) and cough (49.7% [93/187]). Most of the patients did not have complications (82.4% [183/222]), but 8.6% (19/222) of patients developed ARDS. The common treatment administered for COVID-19 was either corticosteroids (33.8% [75/222]), favipiravir (27.0% [60/222]), or remdesivir (23.4% [52/222]) (Table 3). Although most patients (83.8% [181/216]) recovered from COVID-19, 86.9% (186/214) of patients were hospitalised and 43.3% (90/208) required oxygen therapy. Death occurred in 9.0% (20/222) of patients. Overall, 96 patients had progression to severe COVID-19 (Table 3).

COVID-19 outcomes, mortality, the proportion of patients who progressed to severe disease (required oxygen inhalation or died), and the proportion of patients who progressed critical disease (required ventilation or extracorporeal membrane oxygenation, or died) by age groups are shown in Online supplementary Table 1. All these proportions increased with ages from 60s to older than 80 years old; mortality was 8.3% (4/48), 11.5% (6/52), 28.6% (8/28); the proportion of patients who progressed to severe disease was 52.3% (23/48), 59.2% (29/52), and 64.3% (18/28); the proportion who progressed to critical disease was 15.9% (7/48), 16.3% (8/52), 35.7% (10/28) in 60–69, 70–79, ≥ 80 years old, respectively.

Factors associated with progression to severe COVID-19

Comparison of clinical characteristics of 96 patients who progressed to severe COVID-19 (defined as requiring oxygen administration or death) versus 113 patients who did not using univariate analysis is shown in Table 4. Patients who progressed to severe disease were older and had more comorbidities. Especially, hypertension, diabetes mellitus, lung diseases (including COPD/asthma and intestinal lung disease) were more common among the patients who progressed to severe disease. A higher percentage of patients who progressed to severe disease were administered corticosteroids (56.3% [54/96]) than those who did not (38.7% [43/111]).

When adjusting for baseline factors, a multivariable analysis showed that older age (≥ 65 years) (OR 3.52 [95% CI 1.69–7.33], corticosteroid use (OR 2.68 [95% CI 1.23–5.83]), comorbid diabetes (OR 3.56 [95% CI 1.42–8.88]), and lung diseases (OR 2.59 [95% CI 1.10–6.09]) remained independently associated with a greater risk of progression to severe disease (all $P < 0.05$;

Table 1 Demographic and underlying rheumatic disease characteristics ($N=222$)

		n (%)
Age (years), mean ± SD		62.7 ± 14.6
Elderly (≥ 65 years)		104/222 (46.9)
Male		99/222 (44.6)
Current or ex-smoker		84/189 (44.4)
East Asian		219/222 (98.7)
Region	Kanto	166/207 (80.2)
	Chubu	18/207 (8.7)
	Kansai	17/207 (8.2)
	Others	6/207 (2.9)
Medical centre	Clinic	18/206 (8.7)
	General hospital	113/206(54.9)
	University hospital	75/206 (36.4)
Underlying rheumatic disease[a]	Rheumatoid arthritis	107/222 (48.2)
	Gout	32/222 (14.4)
	Systemic lupus erythematosus	18/222 (8.1)
	ANCA-related vasculitis	14/222 (6.3)
	Giant cell arteritis	3/222 (1.4)
	Other vasculitis	7/222 (3.2)
	Sjögren's syndrome	14/222 (6.3)
	Polymyalgia rheumatica	11/222 (5.0)
	Inflammatory muscle disease	7/222 (3.2)
	Adult-onset Still's disease	5/222 (2.3)
	Autoinflammatory syndrome	5/222 (2.3)
	IgG4-related disease	4/222 (1.8)
	Behçet's disease	4/222 (1.8)
	Systemic scleroderma	3/222 (1.4)
	MCTD	2/222 (0.9)
	Sarcoidosis	2/222 (0.9)
	Others[b]	5/222 (2.2)
Disease activity	Remission	114/207 (55.1)
	Low	74/207 (35.8)
	Moderate	14/207 (6.8)
	High	5/207 (2.4)
Comorbidities[a]	None	75/222 (33.8)
	Any comorbid diseases	147/222 (66.2)
	Hypertension	73/222 (32.9)
	Diabetes mellitus	50/222 (22.5)
	Lung diseases	51/222 (23.0)
	COPD/asthma	26/222 (11.7)
	Interstitial lung disease	24/222 (10.8)
	Others	7/222 (3.2)
	Obesity (BMI ≥ 30 kg/m^2)	17/222 (7.7)
	Cerebrovascular/cardiovascular disease	18/222 (8.1)
	Heart disease	13/222 (5.9)
	Cerebrovascular accident	5/222 (2.3)
	Pulmonary hypertension	4/222 (1.8)
	Chronic kidney dysfunction	12/222 (5.4)
	Hepatic disease	9/222 (4.1)
	Malignancy	9/222 (4.1)
	Immunodeficiency	5/222 (2.3)
	Psychiatric disease	5/222 (2.3)
	Psoriasis	2/222 (0.9)

Data are shown as *n* (%) unless otherwise stated

ANCA antineutrophil cytoplasmic autoantibody, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *MCTD* mixed connective tissue disease, *SD* standard deviation

[a]Patients may have had more than one disease

[b]Antiphospholipid antibody syndrome, axial spondylarthritis, psoriatic arthritis, calcium pyrophosphate deposition disease, and Castleman's disease, each reported in 1 patient (0.4%)

Table 2 Medications for underlying rheumatic diseases at the onset of COVID-19 ($N=222$)

	n (%)	Discontinued after the onset of COVID-19 *n* (%)
Corticosteroids	100/220 (45.5)	4/97 (4.1)
Dosage, mg/day (PSL equivalent), median (IQR)	5 (3–9.5)	
bDMARDs	34/222 (15.3)	27/33 (81.8)
TNF inhibitor	9/222 (4.1)	9/9 (100.0)
IL-6 inhibitor	9 (4.1)	5/9 (55.6)
Abatacept	11/222 (5.0)	9/10 (90.0)
IL-17 inhibitor	1/222 (0.5)	1/1 (100.0)
Belimumab	1/222 (0.5)	1/1 (100.0)
Rituximab	3/222 (1.4)	2/3 (66.7)
JAK inhibitors	3/222 (1.4)	3/3 (100.0)
csDMARDs[a]	98/222 (44.1)	64/95 (67.4)
Methotrexate	63/222 (28.4)	53/62 (85.5)
Leflunomide	2/222 (0.9)	2/2 (100.0)
Salazosulfapyridine	28/222 (12.6)	9/25 (36.0)
Bucillamine	6/222 (2.7)	3/6 (50.0)
Immunosuppressants[a]	35/222 (15.8)	16/32 (50.0)
Mycophenolate mofetil	2/222 (0.9)	1/2 (50.0)
Azathioprine	7/222 (3.2)	2/7 (28.6)
Cyclophosphamide	1/222 (0.5)	1/1 (100.0)
Cyclosporine	4/222 (1.8)	2/4 (50.0)
Tacrolimus	22/222 (9.9)	11/22 (57.9)
Others[a]		
Hydroxychloroquine	6/222 (2.7)	0/6 (0.0)
Colchicine	5/222 (2.3)	1/5 (20.0)

Data are shown as *n* (%) unless otherwise stated

COVID-19 coronavirus disease 19, *bDMARDs* biologic disease-modifying antirheumatic drugs, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *IL* interleukin, *IQR* interquartile range, *JAK* Janus kinase, *PSL* prednisolone, *TNF* tumour necrosis factor

[a]Patients may have been on more than one medication

Table 5). Neither underlying rheumatic disease categories, disease activities of rheumatic diseases, nor other medications than corticosteroids for rheumatic diseases showed statistically significant association in this model.

Factors associated with COVID-19-related death

Clinical characteristics of 20 deceased patients were compared to 202 not deceased patients by univariate analysis (Table 6). Patients who died were older (mean ± SD 75.0 ± 13.4 years old) than those survived (61.5 ± 14.2 years old). More patients who died used corticosteroids (70.0% [14/20]) than those who did not (43.0% [86/200]). Higher percentage of patients who died had at least one comorbidity (90.0% [18/20]) than those who did not (63.9% [129/202]). Comorbid chronic kidney dysfunction and hepatic disease were more common among the deceased patients (20.0% [4/20] and 15.0% [3/20]) than the survived patients (4.0% [8/202] and 3.0% [6/202]) (all $P<0.05$).

When adjusting by sex and age using the presence of underlying rheumatic disease or medications for rheumatic disease, a multivariable analysis showed that only older age (≥ 65 years) remained associated with an increased risk of death ($P<0.05$; Online Supplementary Tables 2 and 3).

Discussion

This multicentre, observational study using data from the C19-GRA physician-reported registry of adults with rheumatic diseases and COVID-19 enabled description of the clinical characteristics and management of affected patients in Japan. The COVID-19 characteristics including route of infection, common symptoms, and complications of patients with rheumatic diseases in Japan did not show any obvious different pattern from those of the general populations in Japan and China [21–23]. Treatment pattern for COVID-19 might be different in Japan from western countries. In the USA, hydroxychloroquine and chloroquine were prescribed for COVID-19 frequently under the emergency use authorization because of the potential benefits [24, 25]. In Japan, instead of hydroxychloroquine and chloroquine, it was expected that favipiravir would have an antiviral effect against SARS-CoV-2 [26], and so, favipiravir was frequently administered for COVID-19 in 2020 [21] although it had not been approved for use in patients with COVID-19. In this study, antimalarials such as hydroxychloroquine were administered for only 2.3% (5/222) and 27.0% (60/222) patients were administered favipiravir. In Japan, remdesivir was approved for the treatment of COVID-19 on 7 May 2020 [27], however, because of insufficient drug stocks, it was not widely used at the time. In this study, 23.4% (52/222) were treated with remdesivir.

Regarding COVID-19 outcomes, this analysis showed that both the mortality and severe disease progression were worse with increasing age, which is compatible to the published data from the overall population (i.e., those with and without rheumatic diseases) [21, 22, 28]. While differences in the databases do not allow direct comparison between studies, COVID-19 mortality and proportion of patients who progressed to severe COVID-19 among hospitalized patients in this study were numerically higher than those reported from the general population by the Ministry of Health, Labour, and Welfare (MHLW) in Japan up to 6 January 2021, both overall and in each age group [28]. The MHLW reported mortality 0.0%, 0.0%, 0.1%, 0.3%,

Table 3 COVID-19 characteristics ($N=222$)

	n (%)
Route of infection[a]	
Community acquired, route unknown	105/222 (47.3)
Close contact at home or workplace	107/222 (48.2)
Healthcare-associated infection	17/222 (7.7)
Method of diagnosis[a]	
PCR	204/222 (91.9)
CT	42/222 (18.9)
Antibody test	7/222 (3.2)
Antigen test	17/222 (7.7)
Symptoms present	187/218 (85.8)
Main symptom[a]	
Fever	165/187 (88.2)
Cough	93/187 (49.7)
Shortness of breath	54/187 (28.9)
Malaise	52/187 (27.8)
Complications[a]	
Absent	183/222 (82.4)
ARDS	19/222 (8.6)
Sepsis	3/222 (1.4)
Myocarditis or heart failure	2/222 (0.9)
Secondary infection	9/222 (4.1)
Cytokine storm/similar status (including MAS)	5/222 (2.3)
Treatment for COVID-19[a]	
None (supportive care)	90/222 (40.5)
Corticosteroids	75/222 (33.8)
Favipiravir	60/222 (27.0)
Remdesivir	52/222 (23.4)
Ciclesonide	29/222 (13.1)
IL-6 inhibitor	11/222 (5.0)
Antimalarial agent	5/222 (2.3)
Outcome	
Recovered	181/216 (83.8)
Hospitalised	186/214 (86.9)
Oxygen inhalation	90/208 (43.3)
Ventilator or ECMO	20/208 (9.6)
Death	20/222 (9.0)
Severe disease[b]	96/222 (43.2)
Time to death (days), median (IQR)	17 (11–30)
Time to recovery (days), median (IQR)	13 (10–20)

Data are shown as *n* (%) unless otherwise stated

ARDS acute respiratory distress syndrome, *COVID-19* coronavirus disease 19, *CT* computed tomography, *ECMO* extracorporeal membrane oxygenation, *IL* interleukin, *IQR* interquartile range, *MAS* macrophage activation syndrome, *PCR* polymerase chain reaction

[a]Multiple answers were allowed

[b]Defined as death or oxygen inhalation requirement. In 96 cases, 4 died after oxygen inhalation, 5 died without oxygen inhalation, 1 died but information about oxygen inhalation was missing and 76 required oxygen inhalation but recovered

1.4%, 12.3%, and 1.4% and severe COVID-19 (treated in an intensive care unit or required ventilation or extracorporeal membrane oxygenation) progression 0.0%, 0.0%, 0.5%, 1.4%, 3.0%, 4.1%, 2.0%, and 1.2% in 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, ≥ 80 years old, and overall, respectively. Online supplementary Table 1 shows the most comparable data in our study to the MHLW data, given that we utilised the same age group stratification, a similar definition of progression to severe disease, and close data cut-off date. This numerical difference between the population in our study and the general population accords with a published report of COVID-19 outcome data from immunosuppressed inpatients in Japan, including those with connective tissue diseases and those being treated with immunosuppressive agents, in which a higher proportion of deaths in patients with connective tissue diseases (16.5%) versus non-immunosuppressed patients (3.2%) was found [29]. However, this study did not adjust for other risk factors, including age or sex. A cross-sectional investigation using IORRA cohort in Japan reported that 46 self-reported COVID-19 cases with RA were relatively younger, with lower disease activity and better physical function, compared to 2915 non-COVID-19 with RA cases. Because none of the COVID-19 cases presented pneumonia nor required hospitalization, characteristics of severe COVID-19 cases with RA were not assessed in this report [30].

At the closest cut-off point to our analysis, 6300 cases with underlying rheumatic diseases were registered in the total population of the C19-GRA physician-reported registry globally [31]. Among those, the proportion of elderly people (> 65 years old) was 21.5% (1355/6300), which is lower than our study population which itself was almost half occupied by 65 years and older (46.9% [104/222]). The three most common rheumatic diseases in the global population were rheumatoid arthritis (41.1% [2586/6300]), systemic lupus erythematosus (17.7% [1117/6300]), and psoriatic arthritis (8.3% [522/6300]), in cases registered from Japan, the three most common were rheumatoid arthritis (48.2% [107/222]), gout (14.4% [32/222]), and systemic lupus erythematosus (8.1% [18/222]) (Table 1). The percentage of gout was much lower in the total C19-GRA physician-reported registry population (2.6% [165/6300]). Given a known side effect of favipiravir, a common treatment option for COVID-19 in Japan, is hyperuricemia [32], clinicians tend to specifically check for a history of gout in COVID-19 patients, which may have been a possible explanation for the elevated proportion of patients with gout in this analysis.

While corticosteroids were used by a somewhat higher proportion of patients in the cases from Japan versus the total population usage, biologic DMARD and JAK inhibitor administration at the onset of COVID-19 was lower in Japan than the overall (corticosteroids 45.5% [100/220] versus 33.2% [2094/6300]; biologic DMARDs 15.3% [34/222]

Table 4 Univariate analysis of baseline characteristics of patients who did and did not progress to severe COVID-19

	Did not progress to severe disease ($N=113$)	Progressed to severe disease ($N=96$)	Unadjusted OR (95% CI)[a]	P value[b]
Baseline characteristics				
Age (years), mean ± SD	58.2 ± 15.0	68.4 ± 12.5	1.05 (1.03–1.08)	< 0.001
Elderly (≥ 65 years)	39/113 (34.5)	60/96 (62.5)	3.16 (1.79–5.57)	< 0.001
Male	41/113 (36.3)	53/96 (55.2)	2.16 (1.24–3.77)	0.006
Current or ex-smoker	38/95 (40.0)	39/83 (47.0)	1.33 (0.73–2.41)	0.348
Underlying rheumatic disease[c]				
Inflammatory arthritis	49/113 (20.4)	39/96 (40.6)	0.80 (0.39–1.63)	0.531
Connective tissue diseases/vasculitis	41/113 (36.3)	34/96 (35.4)	0.83 (0.40–1.73)	0.618
Other diseases	23/113 (20.4)	23/96 (24.0)	Ref	-
Disease activity				
Remission	53/104 (51.0)	54/90 (60.0)	Ref	-
Low	42/104 (40.4)	28/90 (31.1)	0.65 (0.36–1.20)	0.173
Moderate	8/104 (7.7)	5/90 (5.6)	0.61 (0.19–2.00)	0.417
High	1/104 (1.0)	3/90 (3.3)	2.94 (0.30–29.21)	0.356
Medications for underlying rheumatic disease				
Corticosteroids	43/111 (38.7)	54/96 (56.3)	2.03 (1.17–3.54)	0.012
Dosage (mg/day (PSL equivalent)), median (IQR)	5 (3.75–10)	5 (2.5–9)	1.02 (0.93–1.12)	0.621
≥ PSL 5 mg/day	26/111 (23.4)	30/96 (31.3)	1.49 (0.80–2.75)	0.207
Medications categories for underlying rheumatic disease[d]				
Without DMARDs/immunosuppressants	46/113 (40.7)	46/96 (47.9)	Ref	-
csDMARDs/immunosuppressants	48/113 (42.5)	38/96 (39.6)	0.79 (0.44–1.43)	0.438
bDMARDs/JAK inhibitors	19/113 (16.8)	12/96 (12.5)	0.63 (0.28–1.45)	0.278
Comorbid underlying disease				
None	55/113 (48.7)	14/96 (14.6)	0.18 (0.10–0.35)	< 0.001
≥ 2	25/113 (22.1)	47/96 (49.0)	3.38 (1.86–6.14)	< 0.001
Hypertension	31/113 (27.4)	39/96 (40.6)	1.81 (1.01–3.23)	0.045
Diabetes mellitus	14/113 (12.4)	34/96 (35.4)	3.88 (1.93–7.80)	< 0.001
Lung diseases[e]	18/113 (15.9)	31/96 (32.3)	2.52 (1.30–4.87)	0.006
Obesity (BMI ≥ 30 kg/m^2)	7/113 (6.2)	9/96 (9.4)	1.57 (0.56–4.38)	0.392
Chronic kidney dysfunction	3/113 (2.7)	9/96 (9.4)	3.79 (1.00–14.44)	0.051
Hepatic disease	3/113 (2.7)	5/96 (5.2)	2.01 (0.47–8.66)	0.346
Malignancy	4/113 (3.5)	4/96 (4.2)	1.18 (0.29–4.87)	0.814
Cerebrovascular/cardiovascular disease	10/113 (8.9)	7/96 (7.3)	0.81 (0.30–2.22)	0.682

Severe COVID-19 was defined as requiring oxygen administration, or death

ANCA anti-neutrophil cytoplasmic antibody, *BMI* body mass index, *bDMARDs* biologic disease-modifying antirheumatic drugs, *COVID-19* coronavirus disease 19, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *CTD* connective tissue disease, *IL* interleukin, *IQR* interquartile range, *JAK* Janus kinase, *OR* odds ratio, *PSL* prednisolone, *Ref* reference value, *TNF* tumour necrosis factor

[a]OR for oxygen administration or death by the univariate logistic regression model

[b]Calculated using the Wilcoxon rank-sum for continuous variables or chi-squared test for categorical variables

[c]Underlying rheumatic diseases were categorised as follows: inflammatory arthritis included rheumatoid arthritis and axial spondylarthritis; connective tissue diseases/vasculitis included systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myopathy, mixed connective tissue diseases, ANCA-associated vasculitis, giant cell arteritis, other vasculitis, Behçet's disease and polymyalgia rheumatica; other diseases included gout, calcium pyrophosphate deposition disease, IgG4-related disease, adult-onset Still's disease, sarcoidosis, antiphospholipid antibody syndrome and Castleman's disease. In cases where a patient had multiple underlying rheumatic diseases, grouping was performed according to the following priority: CTD/vasculitis > inflammatory arthritis > other diseases

[d]Medication categories for underlying rheumatic disease were categorised as follows: without DMARDs/immunosuppressants included no medications for underlying rheumatic diseases, antimalarials (including hydroxychloroquine) or colchicine; csDMARDs included methotrexate, leflunomide, sulfasalazine, and bucillamine; immunosuppressants included azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil/mycophenolic acid and tacrolimus; bDMARDs included TNF inhibitors, IL-6 inhibitors, abatacept, IL-17 inhibitors, belimumab and rituximab. In cases where a patient had multiple medication categories, grouping was performed according to the following priority: bDMARDs/JAK inhibitors > csDMARDs/immunosuppressants > without DMARDs/immunosuppressants

[e]Lung diseases include chronic obstructive pulmonary disease/asthma, intestinal lung disease or others

Table 5 OR of progressing to severe COVID-19 disease by multivariable analysis ($N=222$)

Background factors	Adjusted OR (95% CI)[a]	*P* value[a]
Elderly (≥ 65 years)	3.52 (1.69–7.33)	0.001
Male	1.85 (0.84–4.10)	0.128
Underlying rheumatic disease[b]		
Inflammatory arthritis	0.64 (0.21–1.93)	0.429
Connective tissue diseases/vasculitis	0.40 (0.14–1.18)	0.097
Other diseases	Ref	-
Disease activity		
Remission/low disease activity	Ref	-
Moderate/high disease activity	0.95 (0.29–3.07)	0.930
Corticosteroid administered	2.68 (1.23–5.83)	0.013
Medications categories for underlying rheumatic disease[c]		
Without immunosuppressants	Ref	-
csDMARDs/immunosuppressants	0.88 (0.38–2.02)	0.758
bDMARDs/JAK inhibitors	0.58 (0.18–1.84)	0.356
Comorbidities		
Hypertension	1.36 (0.64–2.89)	0.427
Diabetes mellitus	3.56 (1.42–8.88)	0.007
Lung diseases[d]	2.59 (1.10–6.09)	0.030
Chronic kidney disfunction	2.39 (0.53–10.71)	0.256

ANCA anti-neutrophil cytoplasmic antibody, *BMI* body mass index, *bDMARDs* biologic disease-modifying antirheumatic drugs, *COVID-19* coronavirus disease 19, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *CTD* connective tissue disease, *IL* interleukin, *JAK* Janus kinase, *OR* odds ratio, *PSL* prednisolone, *Ref* reference value, *TNF* tumour necrosis factor

[a]Calculated using the multivariable logistic regression model

[b]Underlying rheumatic diseases were categorised as follows: inflammatory arthritis included rheumatoid arthritis and axial spondylarthritis; connective tissue diseases/vasculitis included systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myopathy, mixed connective tissue diseases, ANCA-associated vasculitis, giant cell arteritis, other vasculitis, Behçet's disease and polymyalgia rheumatica; other diseases included gout, calcium pyrophosphate deposition disease, IgG4-related disease, adult-onset Still's disease, sarcoidosis, antiphospholipid antibody syndrome and Castleman's disease. In cases where a patient had multiple underlying rheumatic diseases, grouping was performed according to the following priority: CTD/vasculitis > inflammatory arthritis > other diseases

[c]Medication categories for underlying rheumatic disease were categorised as follows: without DMARDs/immunosuppressants included no medications for underlying rheumatic diseases, antimalarials (including hydroxychloroquine) or colchicine; csDMARDs included methotrexate, leflunomide, sulfasalazine and bucillamine; immunosuppressants included azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil/mycophenolic acid and tacrolimus; bDMARDs included TNF inhibitors, IL-6 inhibitors, abatacept, IL-17 inhibitors, belimumab and rituximab. In cases where a patient had multiple medications, grouping was performed according to the following priority: bDMARDs/JAK inhibitors > csDMARDs/immunosuppressants > without DMARDs/immunosuppressants

[d]Lung diseases include chronic obstructive pulmonary disease/asthma, intestinal lung disease or others

versus 31.4% [1977/6300]; JAK inhibitors 1.4% [3/222] versus 4.6% [290/6300]). There was a somewhat higher proportion of patients with comorbidities in cases from Japan versus the total population (66.2% versus 50.9% [3207/6300]), while the common comorbid conditions were similar, hypertension (32.9% [73/222] versus 35.1% [2209/6300]), comorbid lung diseases (23.0% [51/222] versus 15.6% [984/6300]), and diabetes mellitus (22.5% [50/222] versus 14.5% [916/6300]) [31].

Among the cases included in the total C19-GRA physician-reported registry population, most recovered (86.2% [5431/6300]), 31.1% (1959/6300) were hospitalised, 28.5% (1795/6300) required oxygen inhalation, 5.1% (324/6300) required a ventilator or ECMO, and 5.8% (362/6300) died [31]. The proportion of cases that resulted in death, hospitalisation, and oxygen or ventilator usage were numerically higher in patients from Japan than the global data; however, these results should be interpreted with caution because of the baseline characteristic difference as mentioned above. Additionally, there is a potential selection bias of patients entered into the C19-GRA physician-reported registry. Moreover, the way that patient information was collected

Table 6 Univariate analysis of baseline characteristics of patients who survived or died from COVID-19 ($N=222$)

	Survived ($N=202$)	Died ($N=20$)	Unadjusted OR (95% CI)[a]	P value[b]
Baseline characteristics				
Age (years), mean ± SD	61.5 ± 14.2	75.0 ± 13.4	1.08 (1.04–1.13)	< 0.001
Elderly (≥ 65 years)	88/202 (43.6)	16/20 (80.0)	5.18 (1.67–16.0)	0.004
Male	90/202 (44.6)	9/20 (45.0)	1.02 (0.40–2.56)	0.969
Current or ex-smoker	78/174 (44.8)	6/15 (40.0)	0.82 (0.28–2.40)	0.718
Underlying rheumatic disease[c]				
Inflammatory arthritis	88/202 (43.6)	9/20 (45.0)	4.60 (0.57–37.47)	0.154
Connective tissue diseases/vasculitis	69/202 (34.2)	10/20 (50.0)	6.52 (0.81–52.71)	0.079
Other diseases	45/202 (22.3)	1/20 (5.0)	Ref	-
Disease activity				
Remission	105/188 (55.9)	9/19 (47.4)	Ref	-
Low	68/188 (36.2)	6/19 (31.6)	1.03 (0.35–3.02)	0.958
Moderate	11/188 (5.9)	3/19 (15.8)	3.18 (0.75–13.52)	0.117
High	4/188 (2.1)	1/19 (5.3)	2.92 (0.29–28.94)	0.361
Medications for underlying rheumatic disease				
Corticosteroids	86/200 (43.0)	14/20 (70.0)	3.09 (1.14–8.38)	0.026
Dosage (mg/day (PSL equivalent)), median (IQR)	5 (3–10)	7.5 (3–9)	1.05 (0.96–1.15)	0.267
≥ PSL 5 mg/day	50/200 (25.0)	9/20 (45.0)	2.45 (0.96–6.27)	0.060
Medications categories for underlying rheumatic disease[d]				
Without DMARDs/immunosuppressants	84/202 (41.6)	9/20 (45.0)	Ref	-
csDMARDs/immunosuppressants	83/202 (41.1)	9/20 (45.0)	1.01 (0.38–2.68)	0.981
bDMARDs/JAK inhibitors	35/202 (17.3)	2/20 (10.0)	0.53 (0.11–2.59)	0.436
Comorbid underlying disease				
None	73/202 (36.1)	2/20 (10.0)	0.20 (0.04–0.87)	0.032
≥ 2	65/202 (32.2)	10/20 (50.0)	2.11 (0.84–5.31)	0.114
Hypertension	68/202 (33.7)	5/20 (25.0)	0.66 (0.23–1.88)	0.434
Diabetes mellitus	44/202 (21.8)	6/20 (30.0)	1.54 (0.56–4.24)	0.404
Lung diseases	45/202 (22.3)	6/20 (30.0)	1.50 (0.54–4.11)	0.436
Obesity (BMI ≥ 30 kg/m^2)	16/202 (7.9)	1/20 (5.0)	0.61 (0.08–4.87)	0.643
Chronic kidney dysfunction	8/202 (4.0)	4/20 (20.0)	6.06 (1.65–22.33)	0.007
Hepatic disease	6/202 (3.0)	3/20 (15.0)	5.761 (1.32–25.12)	0.020
Malignancy	8/202 (4.0)	1/20 (5.0)	1.28 (0.15–10.76)	0.822
Cerebrovascular/cardiovascular disease	16/202 (7.9)	2/20 (10.0)	1.29 (0.27–6.07)	0.746

ANCA anti-neutrophil cytoplasmic antibody, *BMI* body mass index, *bDMARDs* biologic disease-modifying antirheumatic drugs, *CI* confidence intervals, *COVID-19* coronavirus disease 19, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *CTD* connective tissue disease, *IL* interleukin, *IQR* interquartile range, *JAK* Janus kinase, *OR* odds ratio, *PSL* prednisolone, *Ref* reference value, *TNF* tumour necrosis factor

[a]OR for death by the univariate logistic regression model

[b]Calculated using the Wilcoxon rank-sum for continuous variables or chi-squared test for categorical variables

[c]Underlying rheumatic diseases were categorised as follows: inflammatory arthritis included rheumatoid arthritis and axial spondylarthritis; connective tissue diseases/vasculitis included systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myopathy, mixed connective tissue diseases, ANCA-associated vasculitis, giant cell arteritis, other vasculitis, Behçet's disease and polymyalgia rheumatica; other diseases included gout, calcium pyrophosphate deposition disease, IgG4-related disease, adult-onset Still's disease, sarcoidosis, antiphospholipid antibody syndrome, and Castleman's disease. In cases where a patient had multiple underlying rheumatic diseases, grouping was performed according to the following priority: connective tissue diseases/vasculitis > inflammatory arthritis > other diseases

[d]Medication categories for underlying rheumatic disease were categorised as follows: without DMARDs/immunosuppressants included no medications for underlying rheumatic diseases, antimalarials (including hydroxychloroquine) or colchicine; csDMARDs included methotrexate, leflunomide, sulfasalazine, and bucillamine; immunosuppressants included azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil/mycophenolic acid, and tacrolimus; bDMARDs included TNF inhibitors, IL-6 inhibitors, abatacept, IL-17 inhibitors, belimumab and rituximab. In cases where a patient had multiple underlying rheumatic diseases, grouping was performed according to the following priority: bDMARDs/JAK inhibitors > csDMARDs/immunosuppressants > without DMARDs/immunosuppressants

differed from country to country. In Japan, all patients who tested positive for SARS-CoV-2 infection were isolated per the Infectious Disease Control Law and those with underlying conditions, including rheumatic diseases, were recommended for hospitalisation. In 2020, hospital bed capacity allowed them to be hospitalized. Further, polymerase chain reaction testing was reserved for patients with symptoms of COVID-19 or who were in close contact with others experiencing COVID-19 symptoms [33], likely leading to less detection of asymptomatic cases. These differences make direct comparison between countries difficult even from within the same registry.

On the other hand, a meta-analysis of 31 reports of COVID-19 in patients with rheumatic diseases found that COVID-19-related hospitalisation rates were similar in Asia, Europe, and North America (60% [95% CI 41–77%], 62% [51–73%], and 50% [37–64%], respectively) though the fatality rate after hospitalisation was higher in Europe (19% [15–24%]) than in Asia (11% [2–23%]) and North America (12% [6–19%]) [34]. They reported that the rates of oxygen support, intensive care unit (ICU) admission, and death were 33% (95% CI 21–47%), 9% (5–15%), and 7% (3–11%), respectively, in overall, which were similar figures to our findings.

In this study, older age (≥65 years), corticosteroid use, and comorbid diabetes and lung diseases were suggested as possible risk factors for severe COVID-19 outcomes in patients with rheumatic disease, which were reported as association with COVID-19-related hospitalization or death in previous report of C19-GRA cases [11–13], other cohort studies [35–37], and a meta-analysis in patients with rheumatic diseases [38]. Other than these factors we suggested, previous C19-GRA reports suggested that comorbid hypertension/cardiovascular disease and chronic renal insufficiency were associated with higher odds of hospitalisation [11] and male sex and higher disease activity were associated with higher odds of death [13]. In our study, although in the multivariable model male sex and comorbid hypertension did not show a statistically strong association, in univariate analysis, they showed statistically strong association to severe COVID-19. Association of disease activity with severe disease in our study was not clear because the number of cases whose physician reported having higher than moderate disease activity was limited.

Previous reports suggested association of biologic DMARDs with severe COVID-19 outcome [11, 12, 36, 38–40],; however, the relationship of biologic DMARDs or JAK inhibitor usage with COVID-19 outcomes is not clear currently. A report from the first 600 cases from the C19-GRA physician-reported registry suggested that the use of tumour necrosis factor (TNF) inhibitors may reduce the probability of hospitalisation [11]. A later analysis that included 2869 cases from the C19-GRA suggested that JAK inhibitors or rituximab treatment resulted in worse COVID-19 outcomes compared with patients treated with TNF inhibitors, there were no associations between treatment with abatacept or IL-6 inhibitors and COVID-19 severity [12]. This association of JAK inhibitor treatment and worse COVID-19 outcomes was consistent with a New York University cohort study [39], though another cohort study conducted in the USA reported that rituximab users had a higher risk of hospitalisation compared with patients treated with TNF inhibitors and found no significant difference between those treated with JAK inhibitors and TNF inhibitors [40]. These inconsistent results may be explained by differences in confounding factors assessed in analyses or the timing of drug usage during COVID-19. In this analysis, patients receiving biologic DMARDs or JAK inhibitors had lower point estimate for adjusted odds of severe disease progression compared to patients without DMARDs or immunosuppressant,; however, there was no statistical significance (adjusted OR 0.58 [95% CI 0.18–1.84] (Table 5). Although analysis of outcomes according to individual drug classes would be ideal, this was not possible in our study because of limited numbers of patients for such individual drugs. Future studies with larger samples would be more informative.

This current study has several limitations, including a relatively small number of patients and mortality events and a potential for reporting bias of more severe cases. This study is voluntary, and there was a biased distribution with data mainly from tertiary care centres near Tokyo in the Kanto region, which results that our data is not well representative of the whole rheumatology population in Japan and thus limits the generalisability of the results. Additionally, a comparison between our study data from Japan with those from other countries was limited due to selection bias related to different data collection methods, health policy and systems. Finally, this study was based on preliminary data that was collected in 2020, before new variants of COVID-19 (e.g., alpha, delta or omicron) became prevalent, and before COVID-19 vaccines became available in Japan. However, this study allows us to fill the current information gap of the clinical characteristics of COVID-19 among patients with rheumatic diseases in Japan.

In conclusion, this retrospective, multicentre, observational study using data from the C19-GRA physician-reported registry has shown the clinical characteristics of patients with underlying rheumatic disease and diagnosed COVID-19 in Japan. Older age (≥65 years), corticosteroid use and comorbid diabetes and lung diseases are suggested as possible risk factors for severe COVID-19 disease progression.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06305-w.

Acknowledgements We wish to thank the participants of the study (listed on Online Supplementary File). We thank Sarah Bubeck, PhD, and Nila Bhana, MSc (Hons) of Edanz for providing medical writing support.

Author contribution MK conceived the idea of the study and developed the statistical analysis plan and conducted statistical analyses. TN supervised the conduct of this study. MK, MS, HK, SM, SO, and TN contributed to data collection. MK, JA, and TS contributed to the results interpretation. MK drafted the original manuscript. All authors reviewed the manuscript and revised it critically on intellectual content. All authors gave final approval of the manuscript to be published.

Declarations

Conflict of interest MK and JA both are employed by Pharmaceuticals and Medical Devices Agency. The views expressed in this article are those of the authors and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency. TS has received research grants and/or honoraria from Abbvie Japan Co., Ltd., AsahiKASEI Co., Ltd., Astellas Pharma Inc., Ayumi Pharmaceutical, Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo., Eli Lilly Japan K.K., Mitsubishi-Tanabe Pharma Co., Ono Pharmaceutical, Pfizer Japan Inc., Takeda Pharmaceutical Co. Ltd., and UCB Japan Co. Ltd. Tokyo Medical and Dental University received unrestricted research grants for Department of Lifetime Clinical Immunology from AbbVie GK, Asahikasei Pharmaceutical Co., AYUMI Pharmaceutical Corporation, Chugai Pharmaceutical Co., Ltd., CSL Behring K.K., Japan Blood Products Organization, Nippon Kayaku Co., Ltd. and UCB Japan Co. Ltd. SM received consultant fees/speakers fees from Asahikasei Pharma Corp., Ono Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Astellas Pharma Inc. TN received grant/research support from Chugai Pharmaceutical Co., Eisai Co., Ltd., Teijin Pharma Ltd., Eli Lilly Japan K.K., Bristol-Myers K.K., Ono Pharmaceutical Co., Ltd., Asahikasei Pharma Corp., Mitsubishi-Tanabe Pharma Co., Ayumi Pharmaceutical Corporation, Shionogi & Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., AbbVie GK, Nippon Boehringer Ingelheim Co., Ltd., and Taisho Pharmaceutical Co., Ltd., and consultant fees/speakers fees from UCB Japan Co., Ltd., Eisai Co., Ltd., Chugai Pharmaceutical Co., Astellas Pharma Inc., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Asahikasei Pharma Corp., Eli Lilly Japan K.K., Takeda Pharmaceutical Co., Nippon Boehringer Ingelheim Co., Ltd., AbbVie GK., Taisho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., GlaxoSmithKline plc., Kyowa Kirin Co., Ltd., and Mylan N.V. All other coauthors have nothing to declare.

References

1. Fauci AS, Lane HC, Redfield RR (2020) Covid-19—navigating the uncharted. N Engl J Med 382(13):1268–1269. https://doi.org/10.1056/NEJMe2002387
2. Furst DE (2010) The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 39(5):327–346. https://doi.org/10.1016/j.semarthrit.2008.10.002
3. D'Silva KM, Wallace ZS (2021) COVID-19 and rheumatoid arthritis. Curr Opin Rheumatol 33(3):255–261. https://doi.org/10.1097/BOR.0000000000000786
4. Liu Y, Sawalha AH, Lu Q (2021) COVID-19 and autoimmune diseases. Curr Opin Rheumatol 33(2):155–162. https://doi.org/10.1097/BOR.0000000000000776
5. Landewé RBM, Kroon FPB, Alunno A et al (2022) EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. Annals of the rheumatic diseases, annrheumdis-2021–222006. Advance online publication. https://doi.org/10.1136/annrheumdis-2021-222006
6. Nissen CB, Sciascia S, de Andrade D et al (2021) The role of antirheumatics in patients with COVID-19. The Lancet Rheumatology 3(6):e447–e459. https://doi.org/10.1016/S2665-9913(21)00062-X
7. National Institutes of Health (2022) COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/. Accessed 9 July 2022.
8. Robinson PC, Yazdany J (2020) The COVID-19 Global Rheumatology Alliance: collecting data in a pandemic. Nat Rev Rheumatol 16(6):293–294. https://doi.org/10.1038/s41584-020-0418-0
9. Gianfrancesco MA, Hyrich KL, Gossec L et al (2020) Rheumatic disease and COVID-19: initial data from the COVID-19 global rheumatology alliance provider registries. The Lancet Rheumatol 2(5):e250–e253. https://doi.org/10.1016/S2665-9913(20)30095-3
10. Liew JW, Bhana S, Costello W et al (2021) The COVID-19 Global Rheumatology Alliance: evaluating the rapid design and implementation of an international registry against best practice. Rheumatology (Oxford) 60(1):353–358. https://doi.org/10.1093/rheumatology/keaa483
11. Gianfrancesco M, Hyrich KL, Al-Adely S et al (2020) Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 79(7):859–866. https://doi.org/10.1136/annrheumdis-2020-217871
12. Sparks JA, Wallace ZS, Seet AM et al (2021) Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVID-19 Global Rheumatology Alliance physician registry. Ann Rheum Dis 80(9):1137–1146. https://doi.org/10.1136/annrheumdis-2021-220418
13. Strangfeld A, Schäfer M, Gianfrancesco MA et al (2021) Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 80(7):930–942. https://doi.org/10.1136/annrheumdis-2020-219498
14. Ritchie H, Mathieu E, Rodés-Guirao L et al (2022) Coronavirus pandemic (COVID-19). https://ourworldindata.org/coronavirus. Accessed 1 March 2022.
15. Statistics Bureau of Japan, Statistics Handbook of Japan, Ministry of Internal Affairs and Communications, Japan, 2021 (2021) https://www.stat.go.jp/english/data/handbook/pdf/2021all.pdf#page=1. Accessed 1 March 2022.
16. COVID-19 Global Rheumatology Alliance. Rheumatology COVID-19 Provider-Entered Registry (2020) https://rheum-covid.org/downloads/translations/English_rheum-covid-provider-registry.pdf. Accessed 1 March 2022.
17. Wallace ZS, Bhana S, Hausmann JS et al (2020) The rheumatology community responds to the COVID-19 pandemic: the establishment of the COVID-19 global rheumatology alliance. Rheumatology (Oxford) 59(6):1204–1206. https://doi.org/10.1093/rheumatology/keaa191
18. World Health Organization (2022) Clinical management of COVID-19: Living guideline, 23 June 2022. file://vmg-vdi-ad04/redirect(RDS)/b21200wt/Downloads/WHO-2019-nCoV-Clinical-2022.1-eng.pdf Accessed 10 July 2022.

19. Landewé RB, Machado PM, Kroon F et al (2020) EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis 79(7):851–858. https://doi.org/10.1136/annrheumdis-2020-217877
20. Mikuls TR, Johnson SR, Fraenkel L et al (2020) American College of rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 2. Arthritis & rheumatology 72(9):e1–e12. https://doi.org/10.1002/art.41437
21. Matsunaga N, Hayakawa K, Terada M et al (2021) Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: report of the COVID-19 registry Japan. Clin infectious diseases: an official publ Infectious Diseases Soc America 73(11):e3677–e3689. https://doi.org/10.1093/cid/ciaa1470
22. Chen N, Zhou M, Dong X et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395(10223):507–513. https://doi.org/10.1016/S0140-6736(20)30211-7
23. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382(18):1708–1720. https://doi.org/10.1056/NEJMoa2002032
24. Bull-Otterson L, Gray EB, Budnitz DS et al (2020) Hydroxychloroquine and chloroquine prescribing patterns by provider specialty following initial reports of potential benefit for COVID-19 Treatment — United States, January–June 2020. MMWR Morb Mortal Wkly Rep 69:1210–1215. https://doi.org/10.15585/mmwr.mm6935a4
25. Food and Drug Administration (2020) Revocation of the EUA Letter June 15, https://www.fda.gov/media/138945/download Accessed 29 April 2022
26. Wang M, Cao R, Zhang L et al (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30(3):269–271. https://doi.org/10.1038/s41422-020-0282-0
27. Pharmaceuticals and Medical Devices Agency (2020) Special approval for emergency of remdesivir for COVID-19. https://www.pmda.go.jp/english/int-activities/0004.pdf Accessed 1 May 2022.
28. Ministry of Health, Labour and Welfare (2021) Domestic outbreak trends of new coronavirus infections (in Japanese). 2021. https://www.mhlw.go.jp/content/10906000/000716059.pdf. Accessed 1 March 2022.
29. Nomoto H, Suzuki S, Asai Y et al (2022) Clinical characteristics and prognosis of immunosuppressed inpatients with COVID-19 in Japan. J infection chemotherapy: official J Japan Soc Chemotherapy 28(2):224–231. https://doi.org/10.1016/j.jiac.2021.10.021
30. Tanaka E, Inoue E, Abe M et al (2022) Changes in treatment adherence and behaviour during the COVID-19 pandemic in Japanese patients with rheumatoid arthritis: results from cross-sectional study in the IORRA cohort. Modern rheumatology, roab120. Advance online publication. https://doi.org/10.1093/mr/roab120
31. COVID-19 Global Rheumatology Alliance (2020) https://rheum-covid.org/. Accessed 1 March 2022.
32. Mishima E, Anzai N, Miyazaki M et al (2020) Uric acid elevation by favipiravir, an antiviral drug. Tohoku J Exp Med 251(2):87–90. https://doi.org/10.1620/tjem.251.87
33. Sawano T, Kotera Y, Ozaki A et al (2020) Underestimation of COVID-19 cases in Japan: an analysis of RT-PCR testing for COVID-19 among 47 prefectures in Japan. QJM: monthly J Assoc Physicians 113(8):551–555. https://doi.org/10.1093/qjmed/hcaa209
34. Xu C, Yi Z, Cai R et al (2021) Clinical outcomes of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis of global data. Autoimmun Rev 20(4):102778. https://doi.org/10.1016/j.autrev.2021.102778
35. Shin YH, Shin JI, Moon SY et al (2021) Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study. Lancet Rheumatol 3(10):e698–e706. https://doi.org/10.1016/S2665-9913(21)00151-X
36. Ayala Gutiérrez MDM, Rubio-Rivas M, Romero Gómez C et al (2021) Autoimmune diseases and COVID-19 as risk factors for poor outcomes: data on 13,940 hospitalized patients from the Spanish Nationwide SEMI-COVID-19 Registry. J Clin Med 10(9):1844. https://doi.org/10.3390/jcm10091844
37. Freites Nuñez DD, Leon L, Mucientes A et al (2020) Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 79(11):1393–1399. https://doi.org/10.1136/annrheumdis-2020-217984
38. Wang Q, Liu J, Shao R et al (2021) Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. Rheumatol Int 41(5):851–861. https://doi.org/10.1007/s00296-021-04803-9
39. Haberman RH, Castillo R, Chen A et al (2020) COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. Arthritis & rheumatol (Hoboken, N.J.) 72(12):1981–1989. https://doi.org/10.1002/art.41456
40. Raiker R, DeYoung C, Pakhchanian H et al (2021) Outcomes of COVID-19 in patients with rheumatoid arthritis: a multicenter research network study in the United States. Semin Arthritis Rheum 51(5):1057–1066. https://doi.org/10.1016/j.semarthrit.2021.08.010

Authors and Affiliations

Mari Kihara[1,2] · Takahiko Sugihara[3] · Junichi Asano[4,5] · Midori Sato[6] · Hiroshi Kaneko[7] · Sei Muraoka[8] · Shiro Ohshima[9] · Toshihiro Nanki[10]

1 Department of Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan

2 Pharmaceuticals and Medical Devices Agency, Office of Pharmacovigilance II, Tokyo, Japan

3 Graduate School of Medical and Dental Science, Department of Lifetime Clinical Immunology, Tokyo Medical and Dental University, Tokyo, Japan

4 Pharmaceuticals and Medical Devices Agency, Office of New Drug IV, Tokyo, Japan

5 Graduate School of Medical and Dental Sciences, Department of Clinical Biostatistics, Tokyo Medical and Dental University, Tokyo, Japan

6 Department of Respiratory Medicine, National Hospital Organization Tokyo Medical Centre, Tokyo, Japan

7 Division of Rheumatic Disease, National Centre for Global Health and Medicine, Tokyo, Japan

8 Department of Internal Medicine, Ebara Hospital, Tokyo Metropolitan Health and Hospitals Corporation, Tokyo, Japan

9 Department of Clinical Research, National Hospital Organization Osaka Minami Medical Centre, Kawachinagano, Japan

10 Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan