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Original Article

Risk factors for hospitalization or mortality for COVID-19 in patients with rheumatic diseases: Results of a nationwide JCR COVID-19 registry in Japan

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ABSTRACT

Objectives: The incidence and prognosis of Coronavirus Disease 2019 (COVID-19) and rheumatic disease vary among ethnicities and regions. COVID-19 outcomes in rheumatic disease patients remain unclear, especially in the Asia-Pacific region. This study aimed to clarify the demographic and clinical factors that may influence COVID-19 prognosis in rheumatic disease patients.

Methods: This was a case series of patients registered with the COVID-19 national registry of Japan College of Rheumatology between 3 June 2020 and 30 June 2021. Multivariable logistic regression was used to estimate the risk of hospitalization or death. Age, sex, smoking status, rheumatic disease diagnosis, comorbidities, and rheumatic disease medications are taken immediately before infection was analysed.

Results: A total of 220 patients from 55 institutions in Japan were included in the study, among whom 186 (84.5%) were hospitalized and 11 (5.0%) died. COVID-19 treatments were provided to 126 patients (57.3%) and mainly comprised glucocorticoids, favipiravir, remdesivir, and tocilizumab.
In the multiple logistic regression model, older age and a history of hypertension were associated with hospitalization, while older age was associated with mortality. No specific treatment was correlated with mortality or hospitalization by the multivariate analysis.

Conclusions: Older age and hypertension were associated with a poor prognosis in Japanese COVID-19 patients with connective tissue disease. Factors not directly related to connective tissue disease were closely associated with the prognosis.

KEYWORDS: COVID-19; Japan; rheumatic disease; SARS-CoV-2

Introduction

In December 2019, the report of pneumonia of an unknown cause found in Wuhan, Hubei Province, China, spread out to the world. The infection was found to be caused by a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease was named Coronavirus Disease 2019 (COVID-19). COVID-19 spread rapidly all over the world, and on 11 March 2020, the World Health Organization (WHO) declared a pandemic. In Japan, the first case was reported on 15 January 2021, and by June 2021, 0.8 million people (6.7% of the population) had been infected and about 14,700 people had died.

In some cases of SARS-CoV-2 infection, the cytokine storm caused by the immune response to SARS-CoV-2 has been found to cause severe symptoms such as acute respiratory distress syndrome (ARDS). Treatment strategies for COVID-19 include antiviral therapy (e.g. remdesivir and monoclonal antibodies) for cases at risk of severe disease early in the course of infection. In severe cases, immunosuppressive agents such as dexamethasone, baricitinib, and tocilizumab have been shown to be effective and are in clinical use.

These drugs are widely used in daily practice in the field of rheumatic diseases. On the other hand, due to their immunosuppressive effects, patients with rheumatic diseases are generally more susceptible to infections, and some reports suggest that rheumatic diseases may be a risk factor for COVID-19 [1–3].

As a global registry of COVID-19 patients with rheumatic diseases, the Global Rheumatology Alliance (GRA) has

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accumulated more than 9000 cases and has reported high-dose steroid use and rituximab use as risks for disease-modifying anti-rheumatic drug (DMARD) use and COVID-19 severity [4, 5]. However, the majority of cases enrolled in the GRA were from Europe, and only a small percentage (4.4%) were from East Asia, including Japan [6].

In Japan, the COVID-19 Registry Japan (COVIREGI-JP) is a nationwide registry of COVID-19 patients with more than 50,000 cases; however, specific information on rheumatic diseases has not been collected. Therefore, we investigated the risk factors and prognostic factors for severe disease by collecting COVID-19 cases in rheumatic disease patients in Japan.

It is possible that the medical supply system differs between countries and that racial differences also may exist in biological responses to viral infections. Therefore, in this study, we investigated the prognostic factors and risk factors for severe disease by accumulating COVID-19 cases in Japanese patients with rheumatic diseases.

Methods

Setting, study design, and patients

Patients with rheumatic diseases who were receiving treatment at hospitals where rheumatologists belong to the Japanese College of Rheumatology and who were diagnosed with SARS-CoV-2 infection were collected retrospectively. Rheumatologists who treated their own patients for COVID-19 or were informed that their own patients had been diagnosed with COVD-19 provided the information obtained through clinical practice as described below for collection via the web. Study data were collected and managed using Research Electronic Data Capture (REDCap^{TM}) electronic data capture tools hosted at Osaka City University Hospital Centre for Clinical Research and Innovation. REDCap^{TM} is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources. In the present study, we analysed cases enrolled between 3 June 2020 and 30 June 2021.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the Institutional Review Board of Kyushu University (approval number 2020-715) and each participating institution.

We collect anonymous data, but we obtained informed consent from the patient or a substitute, such as a family member, after recovery when possible; COVID-19 infectious and fatal cases were included, and we provided an opt-out on the web page for patients who did not have the opportunity to obtain informed consent.

Variables

We collected the following demographic information: age, gender, pregnancy status, nationality, race, height, weight, smoking history, comorbidities other than rheumatic diseases (pulmonary diseases, diabetes, hypertension, cerebrovascular diseases, renal diseases, malignant tumours, liver diseases, psychiatric diseases, allergic diseases, psoriasis, etc.), and treatment (angiotensin II receptor blocker (ARB) and angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase (PDE)-5 inhibitors, anticoagulants, dialysis, etc.).

Information on the rheumatic disease was collected for rheumatic diseases, including the diagnosis of rheumatic disease and activities of each rheumatic disease according to the physician's clinical judgement, steroid dosage (prednisolone equivalent) at the time of COVID-19 diagnosis, targeted therapies such as biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), and immunosuppressive and immunomodulatory drugs such as csDMARDs.

Diagnostic evidence of COVID-19 (symptoms, computed tomography (CT) imaging, polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), antibody tests, antigen tests, etc.) and exposure to SARS-CoV-2-infected individuals were collected. We collected COVID-19 symptoms (fever, chills, dyspnoea, cough, sputum, sore throat, nasal discharge, diarrhoea, malaise, headache, arthralgia, myalgia, dysgeusia, and dysphagia) at the time of COVID-19 diagnosis and throughout the course of the study.

The history of SARS-CoV-2 vaccination was also collected. Associated symptoms of COVID-19 such as pneumonia, ARDS, pneumothorax, pleural effusion, neurological symptoms, thrombotic symptoms, myocarditis/pericarditis, arrhythmia, sepsis, and cytokine storm/macrophage activation syndrome were collected at diagnosis and throughout the course of the study.

Treatment for COVID-19 included antiviral drugs (remdesivir), anti-inflammatory drugs [glucocorticoids (GCs), IL-6 inhibitors, etc.], anti-infectious drugs (hydroxychloroquine, ivermectin, and azithromycin), convalescent plasma, intravenous immunoglobulin (IVIG), etc., and the impressions of the physicians in charge of each treatment effects were collected.

The outcome of COVID-19 was investigated to determine whether the patient required hospitalization, oxygenation, mechanical ventilation support, intensive care unit admission, extracorporeal membraneous oxygenation use, or death.

The various factors used in the analysis were limited to those that had at least 5% (11 cases) of the total number of positive cases or those factors under 5% but with special analytical interest.

Statistical analyses

Demographic features of the COVID-19 patients with different outcomes (hospitalization and death) were compared using odds ratio (OR) with 95% confidential interval to analyse the correlation of each factor to the outcome. Factors selected for multivariate analysis were mainly those that had been previously reported to be significant, and ORs in the univariate analysis were also used as reference when selecting factors. All Univariable and multivariable multinomial logistic regression models were fitted within STATA Version 17 (STATA Corporation, College Station, TX, USA) to identify both the independent predictors of COVID-19. $p < 0.05$ is defined as statistically significant.

Results

Demographic data of the patients

Two hundred twenty-seven cases were registered from 55 institutions in Japan, and the data were gathered by the

Table 1. Demographic and clinical characteristics of CTD patients with COVID-19 ($n = 220$).

Demographics ($n = 220$)	*N* (%)	Underlying CTD ($n = 220$)	*N* (%)
Female	143 (65.0%)	Systemic sclerosis	10 (4.5%)
Age	61.5 (20-96)	Gout	10 (4.5%)
Age ≧ 65	97 (44.1%)	PM/DM	9 (4.1%)
BMI	24.8 ± 8.1	Bechet's disease	7 (3.2%)
Obesity ($n = 215$)	55 (25.6%)	AOSD	5 (2.3%)
Current smoker ($n = 190$)	24 (12.6%)	Takayasu's arteritis	4 (1.8%)
Comorbidities ($n = 220$)	*N* (%)	GCA	2 (0.9%)
Hypertension	73 (33.2%)	APS	2 (0.9%)
Diabetes mellitus	40 (18.2%)	Others	9 (4.1%)
ILD	24 (10.9%)	CTD activities ($n = 218$)	*N* (%)
Cardiovascular	21 (9.5%)	Remission	111 (50.9%)
COPD	13 (5.9%)	Low activity	81 (37.2%)
Asthma	13 (5.9%)	Moderate activity	21 (9.6%)
Hepatitis	9 (4.1%)	High activity	5 (2.3%)
Post-stroke	5 (2.3%)	CTD medication ($n = 220$)	*N* (%)
ESRD	4 (1.8%)	No DMARD/GC/HCQ	29 (13.2%)
Latent tuberculosis	3 (1.4%)	GC therapy	108 (49.1%)
Liver cirrhosis	2 (0.9%)	PSL ≧ 5 mg/day	53 (24.1%)
PH	2 (0.9%)	PSL ≧ 7.5 mg/day	28 (12.7%)
Underlying CTD ($n = 220$)	*N* (%)	PSL ≧ 10 mg/day	22 (10.0%)
RA	103 (46.8%)	HCQ	14 (6.4%)
SLE	32 (14.5%)	csDMARDs	153 (69.5%)
Spondyloarthritis	12 (5.5%)	b/ts DMARDs	47 (21.4%)
Sjögren's syndrome	12 (5.5%)	b/ts DMARDs only	10 (4.5%)
PMR	11 (5.0%)	csDMARDs no b/tsDMARDs	116 (52.7%)
AAV	11 (5.0%)	csDMARDs + b/tsDMARDs	37 (16.8%)

Obesity: BMI≧25; COPD: chronic obstructive pulmonary disease; PH: pulmonary hypertension; RA: rheumatoid arthritis; AAV: ANCA-associated vasculitis; PM/DM: polymyositis/dermatomyositis; AOSD: adult-onset Still's disease; GCA: giant cell arteritis; APS: anti-phospholipid syndrome; b/ts DMARDs only: b/tsDMARDs without csDMARDs or GC; csDMARDs no b/tsDMARDs: csDMARDs without b/tsDMARDs; ECMO: extracorporeal membraneous oxygenation; ICU: intensive care unit.

Japan College of Rheumatology (JCR) COVID-19 committee member through REDCap™ system. Among them, seven cases were excluded because of their extremely high levels of missing data. The missing data were, at first, inquired from the data manager to each researcher in charge; however, seven relevant cases had not been gained enough data after the inquiries (without any outcome data registered). Thus, the remaining 220 cases were further analysed of their demographic data and the outcome.

Among 220 cases, all but two patients were native Japanese (one East Asian and one Latino race) and 168/220 (76.4%) have not been registered in other COVID-19 patient registries including GRA or COVIREGI-JA.

The demographic and clinical features of the patients are described in Table 1. The 143/220 (65.0%) patients were female. The median age of the patients was 61.5 (20–96), and 97/220 (44.1%) of the patients were in the age range equal to or above 65 years. There was no pregnant patient. The body mass index (BMI) was 22.6 ± 8.2, and obesity (BMI > 25) was observed in 55/215 patients (25.6%). There were 25 current smokers (13.1%; smoking status registered in 191 patients).

The most prevalent comorbidity was hypertension ($n = 73$, 33.2%), followed by diabetes ($n = 40$, 18.2%), interstitial lung disease (ILD; $n = 24$, 10.9%), cardiovascular diseases ($n = 21$, 9.5%), chronic obstructive lung disease ($n = 13$, 5.9%), and asthma ($n = 13$, 5.9%). Overall, one or more underlying lung diseases were diagnosed in 53/220 (24.1%). There were five (2.3%) post-stroke patients and four (1.8%) end-stage renal disease (ESRD) patients.

The most common connective tissue disease (CTD) was rheumatoid arthritis (RA; $n = 103$, 46.8%), followed by systemic lupus erythematosus (SLE; $n = 32$, 14.5%), spondyloarthritis ($n = 12$, 5.5%), Sjögren's syndrome (SS; $n = 12$, 5.5%), polymyalgia rheumatica (PMR; $n = 11$, 5.0%), ANCA (anti-neutrophil cytoplasmic antibody)-associated vasculitis (AAV; $n = 11$, 5.0%) and systemic sclerosis ($n = 10$, 4.5%). The activities of the underlying CTD were analysed in 218 patients and reported as high in 111 (50.9%), moderate in 81 (37.2%), mild in 21 (9.6%), and remission in 5 (2.3%) patients. In 191/220 (86.8%) patients, CTD were treated with DMARDs and/or GC and/or hydroxychloroquine (HCQ). GC therapy was reported in 108/220 (49.1%) CTD patients prior to the COVID-19 and treatments with csDMARDs, bDMARDs, and tsDMARDs were reported in 153 patients (69.5%), 49 patients (22.3%), and 7 patients (3.2%), respectively. In 14/220 (6.4%), HCQ was administered.

The time to symptom onset to diagnosis for COVID-19 was 3.5 days (0–33 days; 19 missing data). None but one patient was reported to be vaccinated for SARS-CoV-2.

Symptoms of COVID-19 are listed in Table 2. The symptoms were similar to the reported symptoms of COVID-19 in the general population [6]. There were 34/220 cases (15.5%) with associated complications (including cases with overlapping the complications); concomitant infections were reported in 18/218 (8.3%; bacterial pneumonia 10, viral pneumonia 6, fungal infection 2, sepsis 1; overlapped), ARDS in 8/218 (3.7%), pleural effusion in 5/213 (2.3%), and macrophage activating syndrome in 5/213 (2.3%). There were no thrombotic or haemorrhagic events reported.

Table 2. The symptoms and the treatments of the COVID-19.

Symptoms ($n=220$)	N (%)	Complications ($n=218$)	N (%)
Fever	137 (62.3%)	Concomitant infection	18 (8.3%)
38°C≦	97 (44.1%)	Bacterial infection	10 (4.6%)
38°C>	40 (18.2%)	Viral infection	6 (2.8%)
Cough	113 (51.4%)	Fungal infection	2 (0.9%)
Fatigue	112 (50.9%)	Sepsis	1 (0.5%)
Dyspnoea	53 (24.1%)	ARDS	8 (3.7%)
Sore throat	43 (19.5%)	Pleural effusion ($n=213$)	5 (2.3%)
Sputum	39 (17.7%)	MAS ($n=213$)	5 (2.3%)
Headache	30 (13.6%)	Treatment ($n=220$)	N (%)
Chill	29 (13.2%)	GC	85 (38.6%)
Arthritis	29 (13.2%)	Favipiravir	48 (21.8%)
Rhinitis	27 (12.3%)	Remdesivir	46 (20.9%)
Dysosmia	23 (10.5%)	Ciclesonid	18 (8.2%)
Dysgeusia	22 (10.0%)	Tocilizumab	15 (6.8%)
Diarrhoea	20 (9.1%)		
Muscle pain	16 (7.3%)		

Symptoms or associated complications recognized and the treatments performed during the disease courses are shown. MAS: macrophage activating syndrome.

Table 3. Outcomes of the COVID-19 ($n=220$).

Outcome	N (%)
Hospitalized	186 (84.5%)
Oxygen therapy	70 (31.8%)
Mechanical ventilation	18 (8.2%)
ECMO	1 (0.5%)
ICU	22 (10.0%)
Deceased	11 (5.0%)

Oxygen therapy: induction of any type of oxygen inhalation therapy; ECMO: induction of extracorporeal membrane oxygenation; ICU: admission to the intensive care unit.

COVID-19 treatments with oral and intravenous/subcutaneous reagents were performed in 126/220 patients (57.3%). Most prevalent treatment was GC ($n=85$: 38.6%) followed by favipiravir ($n=48$; 21.8%), remdesvir ($n=46$, 20.9%), ciclesonid ($n=18$, 8.2%), and tocilizumab ($n=15$; 6.8%). The effect of these reagents was evaluated by each researcher with the visual analogue scores. The visual analogue scores were 70 (0–100) for GC, 43 (0–89) for favipiravir, 55 (0–100) for remdesivir, 50 (0–80) for ciclesonid, and 80 (2–100) for tocilizumab (data not shown in the table).

The outcome of COVID-19

The outcome of COVID-19 is shown in Table 3. 186/220 (84.5%) were hospitalized, 70/220 (31.8%) were on oxygen therapy (18 on mechanical ventilation and one on extracorporeal membraneous oxygenation), and 11 (5.0%) patients deceased from the COVID-19. Twenty-two patients were admitted to the intensive care unit during their hospitalization.

The characteristic features of the hospitalized patients ($n=186$) were compared with the non-hospitalized patients ($n=34$) (Table 4). The older age, male, coexistences of complications (hypertension, diabetes, or cardiovascular diseases), prednisolone (PSL) ≧ 10 mg/day, b/ts DMARD monotherapy, HCQ, or csDMARD treatments were considered as a candidate factors related to the hospitalization referring to the past reports or the ORs of the current univariate analyses. The multivariable logistic regression analyses using statistically significant factors in univariate analyses ($p<0.05$) revealed older age and the coexistence of hypertension as the risk factors for hospitalization. The multiple regression model failed to analyse PSL ≥ 10 mg/day as a risk factor in a multiple logistic regression with hospitalization as the outcome due to the sparce and biased population of the data (Table 4).

The characteristic features of the 11 deceased patients were compared with the survived patients ($n=209$) (Table 5). Among 11 deceased patients, the underlying CTD were five RA, three PMR, and one for giant cell arteritis, ANCA-associated vasculitis, and SS. Eight patients were on PSL [median 4 mg/day (0–25 mg/day)] and two were over 10 mg/day. None of the patients were treated with bDMARDs nor with tsDMARDs.

'The higher age, coexistence of ILD, PMR as background CTD, current smoking, and oxygen therapies were assumed as candidate factors that related to the death referring to the past reports or the ORs of the current univariate analyses. The multivariable logistic regression analyses using these factors revealed that older age resulted as a significant risk factor for death' (Table 5).

Discussion

This is the first national report on the demographics and outcomes of COVID-19 in CTD patients in Japan. This study analysed the patients registered before 30 June 2021. All of the registered cases in the study were un-vaccinated for SARS-CoV-2; as in Japan, the vaccination for SARS-CoV-2 in the general population started in April 2021. As the health care expenditures for COVID-19 are fully covered by the national health insurance, the hospitalization of COVID-19 patients, especially immunocompromised patients, is usual practice, thus leading to the high percentage of hospitalization in our study.

Intriguingly, the proportion of the underlying CTD was similar in our patients compared to the past report from the GRA registry [10]. RA followed by SLE, spondyloarthritis, SS, and vasculitis are in concordance with the GRA data with a similar prevalence rate. Considering the incidence rate of CTD, the high rate of SLE patients in our COVID-19 registry suggests that SLE is more prone to being affected by SARS-CoV-2. In fact, the predisposition to viral infection in patients with SLE is often reported describing its abnormal type I interferon secretion or other immunopathogenic mechanism overlapping with the deleterious hyper-inflammation response in the viral infection [7, 8, 13]. However, all but one SLE patient have recovered, and the rates of hospitalization (25/32; 78.1%), oxygen therapy (10/34; 29.4%), or respirator use (3/32; 9.4%) were comparable to those rates in the whole study population. Although methodological limitations make it difficult to determine the actual outcomes of COVID-19 in patients with SLE, there are reports of similar results on this topic. A multi-centre retrospective analysis from Italy revealed that 46/51 (90.2%) of SLE patients with SARS-CoV-2 infection showed asymptomatic or mild disease without pneumonia [9], and the relatively higher intensity of the immunosuppressive treatment was insisted as a rationale for

Table 4. Factors related to the hospitalization in COVID-19-affected CTD patients.

	Hospitalized	Not-hospitalized	Univariate	Multivariate	
	($n = 186$)	($n = 34$)	Odds ratio (95% CI)	Odds ratio (95% CI)	p value
Age	63 (21–96)	53.5 (20–70)	1.04 (1.02–1.07)$^{\natural}$	1.03 (1.01–1.06)$^{\natural}$	0.021
Male	71 (38.2%)	6 (17.6%)	2.88 (1.16–7.10)	2.18 (0.80–5.90)	0.13
BMI	22.5 (14.5–34.8)	22.9 (16.9–31.2)	0.98 (0.90–1.89)$^{\natural}$		
Obesity	48/180 (26.7%)	8 (23.5%)	1.18 (0.51–2.73)		
Current smoker	20/157 (12.7%)	5 (14.7%)	0.85 (0.303–2.35)		
HTN	69 (37.1%)	4 (11.8%)	4.42 (1.56–12.5)	3.15 (1.00–10.1)	0.05
DM	38 (20.4%)	2 (5.9%)	4.11 (0.94–17.9)		
CVD	21 (11.3%)	0	∞ (1.11–∞)		
ILD	23 (12.4%)	1 (2.9%)	4.66 (0.77–27.9)		
COPD	13 (7.0%)	0	∞ (0.65–∞)		
RA	91 (48.9%)	12 (35.3%)	1.76 (0.83–3.71)		
SLE	25 (34.0%)	7 (20.6%)	0.60 (0.24–1.48)		
SpA	10 (5.4%)	2 (5.9%)	0.91 (0.21–3.84)		
SS	9 (4.8%)	3 (8.8%)	0.53 (0.14–1.89)		
PMR	11 (5.9%)	0	∞ (0.54–∞)		
AAV	9 (4.8%)	2 (5.9%)	0.81 (0.19–3.48)		
SSc	9 (4.8%)	1 (2.9%)	1.68 (0.26–10.5)		
Gout	9 (4.8%)	1 (2.9%)	1.69 (0.26–10.5)		
Disease activity	92/71/18/4	19/10/3/1	0.77 (0.37–1.60)/1.48 (0.58–3.23)/0.59 (0.19–2.01)/0.73 (0.10–4.94)		
PSL intake	79	17	0.74 (0.36–1.52)		
PSL $\geqq$ 5 mg/day	47 (25.3%)	6 (17.6%)	1.58 (0.63–3.93)		
PSL $\geqq$ 7.5 mg/day	26 (14.0%)	2 (5.9%)	2.60 (0.65–10.3)		
b/tsDMARDs	38 (20.4%)	11 (32.4%)	0.54 (0.24–1.18)		
csDMARDs	136 (73.1%)	17 (50.0%)	2.72 (0.175–0.768)	1.09 (0.46–2.61)	0.85
b/tsDMARDs W/o csDMARDs	13 (7.0%)	7 (20.6%)	0.29 (0.11–0.77)	0.89 (0.22–3.51)	0.86
b/tsDMARDs only	7 (3.8%)	4 (11.8%)	0.29 (0.086–0.99)		
HCQ	9 (4.8%)	5 (14.7%)	0.30 (0.096–0.900)	0.52 (0.13–2.01)	0.34

Odds ratio with 95% confidential interval (95% CI) and the p values (Fisher's exact test) were used to analyse the correlation of each factor to the outcome. The multivariate analysis was performed based on the factors that are selected referring to the past reports or the ORs of the current univariate analyses. Obesity: BMI > 25; HTN: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; RA: rheumatoid arthritis; SpA: spondyloarthritis; AAV: ANCA-associated vasculitis; SSc: systemic sclerosis; disease activity: underlying CTD disease activity shown as the numbers of remission/mild/moderate/high; b/ts DMARDs: biologic or targeted synthetic disease-modifying rheumatic drugs; csDMARD: conventional synthetic DMARDs; b/tsDMARDs only: b/tsDMARDs treatment without csDMARDs nor GCs; NS: not significant; $^{*}p < 0.05$ $\natural$indicates the odds ratio for a one-unit change in a risk factor.

the suppression of COVID-19 activity. The telemedicine survey from Italy unveiled a higher incidence rate of COVID-19 compared to the rate of the general population [10]. The propensity score matching analysis from the USA reported that the mortality rate of COVID-19 in SLE patients was compatible with those in the general population [11]. In a study from South Korea [12], 365 PCR-positive CTD patients were identified from receipt data and investigated using propensity score matching. In this cohort study, CTD patients were more likely to develop SARS-CoV-2 positive and were associated with an increased risk of COVID-19 severity and mortality. High-dose steroid use was associated with an increased risk of COVID-19 severity and death, but DMARDs had no association. Unlike our study, the CTD diagnosis may be inaccurate because of the receipt-based study; COVID-19 symptoms and other information were not collected. [12]

GCs might be associated with worse outcomes in individuals with COVID-19 in individuals with CTD, but some immune suppressants or DMARDs do not appear to significantly increase the risk of contracting COVID-19 or poor subsequent outcomes [13]. The ethnicity, age, and comorbidities such as hypertension or diabetes are reported to have a comparatively higher impact on the prognostic outcome of COVID-19 in autoimmune patients [4, 14, 15]. In our registry, patients with SLE were 54.5 (20–95) years old, compatible with a lower rate of comorbidities [diabetes 3/32 (9.4%) and hypertension 9/32 (28.1%)] with lower GC dose [PSL 3 (0–17) mg/day] compared to the data of the CTD patients in general.

The complex interaction between SARS-CoV-2 infection and defected immune system in patients with SLE may have particular implications; however, its clarification and further exploration should be needed.

We found that hospitalization of the COVID-19-affected CTD patients was higher in patients with older age and the coexistence of hypertension in the multiple logistic regression analysis. Other possible risk factors, or those that showed statistical significance in the univariate analysis, were not evident in the multifactor analysis. The favourable effect of b/tsDMARD monotherapies was reported in the previous articles [13]. However, our data failed to show a significant correlation with the hospitalization in the multivariate analysis.

Table 5. Factors related to the mortality in COVID-19-affected CTD patients.

	Deceased	Survived	Univariate	Multivariate	
	($n = 11$)	($n = 209$)	Odds ratio (95% CI)	Odds ratio (95% CI)	p value
Age	86 (61–92)	61 (21–96)	1.15 (1.07–1.23)$^{\phi}$	1.14 (1.05–1.23)$^{\phi}$	0.001*
Male	5 (45.5%)	72 (34.4%)	1.59 (0.50–1.58)		
BMI	20.5 (16.5–26.8)	22.2 (14.5–34.8)	0.92 (0.78–1.08)$^{\phi}$		
Obesity	1/10 (10%)	55/204 (27.0%)	0.27 (0.04–1.69)		
Current smoker	0/11	25/180 (13.9%)	0.00 (0.00–2.23)		
HTN	3 (27.3%)	70 (33.5%)	0.75 (0.21–2.68)		
DM	4 (36.4%)	36 (17.2%)	2.75 (0.82–9.31)		
CVD	2 (18.2%)	19 (9.1%)	2.22 (0.51–9.34)		
ILD	4 (36.4%)	20 (9.6%)	5.40 (1.55–19.0)	2.35 (0.517–10.65)	0.269
COPD	0	13 (6.2%)	0.00 (0.00–5.53)		
RA	5 (45.5%)	98 (46.9%)	0.94 (0.30–3.01)		
SLE	0	32 (15.3%)	0.00 (0.00–1.98)		
SpA	0	12 (5.7%)	0.00 (0.00–6.04)		
SS	1 (9.1%)	11 (5.3%)	1.80 (0.28–12.2)		
PMR	3 (27.3%)	8 (3.8%)	9.4 (2.90–39.8)	1.26 (0.194–8.19)	0.809
AAV	1 (9.1%)	10 (4.8%)	1.99 (0.31–13.5)		
SSc	0	10 (4.8%)	0.00 (0.00–7.37)		
Gout	0	10 (4.8%)	0.00 (0.00–7.37)		
Disease activity	7/3/1/0	104/78/20/5	1.77 (0.53–5.82)/0.63 (0.18–2.26)0.95 (0.15–6.12)/0.00 (0.00–15.5)		
PSL intake	8 (72.7%)	100 (47.8%)	2.91		
PSL ≧ 5 mg/day	3 (27.3%)	50 (23.9%)	1.19 (0.33–4.33)		
PSL ≧ 7.5 mg/day	2 (18.2%)	26 (12.4%)	1.56 (0.36–6.858)		
PSL ≧ 10 mg/day	2 (18.2%)	20 (9.6%)	2.10 (0.482–9.355)		
b/tsDMARDs	0	49 (23.4%)	0.00 (0.00–1.16)		
csDMARDs	8 (72.7%)	145 (69.4%)	1.78 (0.33–4.22)		
b/tsDMARDs W/o csDMARDs	0	20 (9.6%)	0.00 (0.00–3.42)		
b/tsDMARDs only	0	11 (5.3%)	0.00 (0.00–6.64)		
HCQ	0	14 (6.7%)	0.00 (0.00–5.10)		
ICU	3 (27.3%)	19 (9.1%)	3.75 (1.00–14.32)		
Respirator	2 (18.2%)	16 (7.7%)	2.68 (0.61–12.1)		
Oxygen therapy	9 (81.8%)	61 (29.2%)	10.7 (2.25–31.1)	5.36 (0.74–38.9)	0.10
GC for COVID	8 (72.7%)	77/207 (37.2%)	4.50 (1.25–16.1)	0.33 (0.05–2.24)	0.26
Remdesivir	3 (27.3%)	43/207 (20.8%)	1.43 (0.398–5.219)		
Tocilizumab	0	15/207 (7.2%)	0.00 (0.00–4.72)		

Odds ratio with 95% confidential interval (95% CI) and the p values (Fisher's exact test) were used to analyse the correlation of each factor to the outcome. The multivariate analysis was performed based on the factors that are selected referring to the past reports or the ORs of the current univariate analyses. Obesity: BMI > 25; HTN: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; RA: rheumatoid arthritis; SpA: spondyloarthritis; AAV: ANCA-associated vasculitis; SSc: systemic sclerosis; GCA: giant cell arteritis; disease activity: underlying CTD disease activity shown as the numbers of remission/mild/moderate/high; b/ts DMARDs: biologic or targeted synthetic disease-modifying rheumatic drugs; csDMARD: conventional synthetic DMARDs; b/tsDMARDs only: b/tsDMARDs treatment without csDMARDs nor GCs; GC for COVID: GC therapy for COVID-19; remdesivir: remdesivir treatment for COVID-19; tocilizumab; tocilizumab treatment for COVID-19; NS: not significant; *$p < 0.05$; $^{\phi}$indicates the odds ratio for a one-unit change in a risk factor.

Most of our cases recovered from the disease; however, the mortality rate of 4.7% is not at a low level compared to the accumulating rate of the general population at the time (1.85%)]16]. When restricting to the hospitalized patients in our registry, the mortality rate was similar to that in the Japanese general population reported as 7.5% (197/2634; reported in COVIREGI-JP) [17]. The risk factor for mortality extracted by the multivariate analyses was higher age. Lower BMI, current smoking, coexistence of ILD, PMR, or steroid intake did not show a correlation with death in the multiple logistic regression analysis.

It is previously reported that the factors not directly related to CTD (such as age >65, hypertension, diabetes, lung disease, and ESRD) are more closely associated with the prognosis of COVID-19 in CTD patients, and the specific CTD or their treatments are less related to refs [13] and [18]. Our results are along with their findings. Hypertension was correlated to the hospitalization in our data. Although there are previous reports that hypertension correlates with the prognosis of COVID19 and can therefore be viewed as a risk factor, the underlying mechanisms are often unclear. In general, it has been suggested that COVID-19, which is particularly active, is considered a vasculopathy, and hence, hypertension as an underlying disease may boost vascular damage. Alternatively, other than adjusted factors, such as renal impairment, may influence prognosis as mediators. We have reviewed data on ESRD but found very few (4/220) and no statistically significant differences between the patients with and without admission in univariate analysis. ESRD was not included in the table as an association factor as the number of the

patients was small under 5% (11 cases). The disease severity of CTD did not correlate to the poor prognosis in our registry. Generally, the disease activity of CTD is a known factor in affecting or worsening the infection [19–21] as well as in COVID-19; however, the importance of lowering CTD activity in prophylaxis or preventing the worsening of COVID-19 [22, 23] may be masked in our patients' data. There may be a slight possibility that cases with high disease activity were not reported specifically for some reason. Alternatively, it is possible that Japan's strict social isolation policy especially for the COVID-19-risked population has worked well to reduce the risk of infection, among highly disease-active patients, through the limitations such as prevention of outings and contact with others. In any case, it is difficult to identify the cause of the finding, and we cannot deny the risk of not capturing the whole picture of the CTD-COVID19 patients, especially high-risk cases, and consider this to be one of the possible limitations of the study.

There are several additional limitations in this study. First of all, as this registry is voluntary, not all cases are captured in this study. Caution is needed to discuss the prevalence or the causal inference of COVID-19 in CTD patients from our data. Secondly, the social environment between the different epidemic periods is not fully discussed, such as the mutant strains with a more severe prognosis or the newly emerged reagents for COVID-19 treatment may have influenced the prognosis of the patients. In fact, at the beginning of June 2021, the positive rate of the B.1.617.2 lineage variant (delta variant), the variant which is suggested to be more infectious than the B.1.1.7 lineage variant (alpha variant), was still at a low level of 5%, nationwide in Japan [24]. Thirdly, the analysis of risk factors was obtained by combining various disease groups with diverse pathological presentations into a single group; thus, caution must be exercised in interpreting the results. Although it would have been desirable to perform sub-analyses based on various factors such as underlying diseases or years since disease onset, those analyses were difficult due to the limited number of cases. Finally, in the multiple logistic regression with hospitalization as an outcome, it was not possible to evaluate PSL $\geq$ 10 mg/day as a risk factor due to the strong bias and sparsity of the data. This is a phenomenon that is occasionally observed and is one of the limitations of this study.

In this series of CTD patients with COVID-19, we did not find particular disease or therapeutic reagents that correlated to the poor prognosis in the multiple variant analyses. Rather, as in the general population, CTD patients who are older and/or have comorbidities had higher odds of COVID-19-related hospitalization or death.

In this study, a group of patients with miscellaneous backgrounds was analysed demographically as a CTD, but comparisons with the general population may bring out more of its characteristics. Alternatively, the analysis of each CTD may highlight risk factors and processes that are characteristic of each disease. This registry is still in operation, and a more detailed analysis is planned for future reports.

Conflict of interest

K.O., Y.K., T.H., M.Y., Y.K., M.O., and T.A. have no conflicts of interest to declare. T.T. has received a speaking fee from Eli Lilly Japan K.K. and a research grant from Chugai Pharmaceutical Co.

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