

Original Article

Decrease of infectious complications in outpatients with autoimmune diseases from 2019 to 2020 under the COVID-19 pandemic: A single-center, retrospective cohort study in Japan

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Abstract

Objective: To examine how the novel coronavirus disease (COVID-19) has changed infectious complications in outpatients with autoimmune diseases. **Methods:** We performed a retrospective, record-linked cohort study and questionnaire about lifestyle changes in patients who visited our department in 2019 and 2020. **Results:** We surveyed 1316 outpatients in 2019 and 1284 in 2020. The most common underlying diseases were rheumatoid arthritis (842 vs. 814) and systemic lupus erythematosus (126 vs. 127). No significant difference in median age (66 vs. 67 years), respiratory comorbidities (30.4% vs. 32.0%), or corticosteroid use (42.2% vs. 44.3%) was found between the years. Immunomodulating agents were used more in 2020 (33.1% vs. 39.7%, $p<.001$). Total number of infections (28.0/100 vs. 19.4/100 person-years), pneumonia (3.6 vs. 1.6), influenza (2.1 vs. 0.1), and

non-viral dermatological infections (3.8 vs. 2.1) were significantly lower in 2020. No significant difference was found for herpes zoster (2.2 vs. 1.8), urinary tract infections (3.3 vs. 3.8), or gastrointestinal infections (2.9 vs. 3.0). According to the questionnaire, 75% of the respondents became more conscious about wearing masks and 81% began to use hand sanitizer during the pandemic. **Conclusion:** Under the COVID-19 pandemic, some infectious complications have decreased in outpatients with autoimmune diseases.

Introduction

A novel coronavirus, termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was isolated as a pathogen of contagious pneumonia with high fatality in 2019 [1]. The novel coronavirus disease (COVID-19) spread globally, causing thousands of deaths and enormous impacts worldwide. The World Health Organization prevention guidelines advised protective behavior for individuals such as wearing masks properly, washing hands, hand hygiene, maintaining social distancing, avoiding the 3Cs (spaces that are closed, crowded, or involve close contact), and avoiding touching the facial mucosa [2]. In Japan, the first patient with COVID-19 was reported on January 2020, after which mask wearing and hand hygiene increased. In March 2020, the Japanese government directed the temporary closing of schools and recommended that companies should work from home. In Miyagi prefecture, which has about 2.8 million inhabitants and where our hospital is located, the first reverse transcription-polymerase chain reaction amplification (RT-PCR) positive SARS-CoV-2 case was detected on 29, February 2020. Public schools were closed between March 2020 and May 2020, residents greatly increased their vigilance during this period. After that, no positivity was detected in May 2020 and the state of emergency was lifted, but SARS-CoV-2 infection was detected again in June 2020, and increased thereafter. Over 100 positive cases/week were detected from October 2020 to January 2021 in Miyagi, according to the Miyagi Prefectural Government website, <https://www.pref.miyagi.jp/uploaded/attachment/837324.xlsx>. As of May 2021, the COVID-19 pandemic has persisted and mask wearing, hand hygiene measures, and social distancing have continued.

Previous random controlled trials (RCT) and meta-analyses have concluded that these measures might also have protected people from various infections other than COVID-19 [3–9], although opinions differ among these authors regarding the most effective measures. Numerous studies that have reported a decrease in influenza and other respiratory infections after the COVID-19 pandemic concluded that public health efforts to control COVID-19 might have reduced the spread of viral respiratory diseases [10–12].

In addition, many pathogens are known to inhibit infection with other pathogens in the same host [13, 14]. COVID-19 itself may interfere with other infections virologically.

Controlling infectious complications has been an important issue for the care of patients with autoimmune diseases, who tend to be immunocompromised due to multiple factors as well as their immune system, including related organ damage and therapies such as immunosuppressive drugs [15–18]. The effectiveness of general measures against infection may differ between these patients and those in the healthy population; however, no large-scale trial has investigated this possibility. Moreover, nationwide changes in lifestyle and the social environment after the COVID-19 pandemic may have had a different impact on patients with autoimmune diseases than in the healthy population.

We performed a retrospective cohort study to investigate the status of infectious complications in outpatients with autoimmune diseases using patients' medical records in 2019 and in 2020; i.e., before and after the COVID-19 pandemic.

Methods

We conducted a retrospective, record-linked cohort study among patients who regularly visited the rheumatology outpatient department at Tohoku Medical and Pharmaceutical University Hospital in 2019 and 2020. Each patient met the criteria defined by the Ministry of Health, Labor and Welfare for Japan or international consensus [19–26]. Because wearing masks became more common in Japan after February 2020, we categorized the patients into the following two groups. Group 2019 included outpatients who had visited the department of rheumatology for routine monitoring prior to 31 January 2019 and who had been followed up at an interval of 12 weeks or less until 31 January 2020. Group 2020 included outpatients who had visited prior to 31 January 2020 and who had been followed up until 31 January 2021. Patients who discontinued regular visits were excluded from the analyses to eliminate seasonal bias between Group 2019 and Group 2020. Patients who discontinued visits because of an infectious complication (death or long hospitalization) were counted separately from the analyses. Data regarding infectious disease complications and their classifications were collected from patients' medical records. Influenza and pneumonia were laboratory-confirmed, and the incidence of other infections such as bronchitis, dermatological infections, and gastrointestinal infections was recorded according to the assessments of the attending doctors. Data for the common cold were excluded from analyses because it is highly dependent on the patient's self-declared symptoms. To assess behavioral changes before and after the COVID-19 pandemic, patients who visited our rheumatology outpatient department between 1 April 2020 and

30 June 2020 were asked to complete an anonymous questionnaire about their infection-prevention behaviors. One of three response choices could be selected for each survey item: 1) I have always been as careful as I am now, 2) I have done this much more recently, 3) I never (or cannot) perform this action.

This study was approved by the ethics committee of the Tohoku Medical and Pharmaceutical University Hospital (#2019-2-230/2020-2-142/2021-2-011). Opt-out consent for the use of anonymized medical data and written informed consent for the disclosure of questionnaire results were obtained from all patients.

Statistical analysis

The frequencies and percentages of categorical variables were compared using chi-square test. Binary logistic regression model was applied for multivariate analysis. All analyses were performed using BellCurve for Excel (Social Survey Research Information, Tokyo, Japan). A two-tailed $p < .05$ was considered statistically significant.

Results

Patient characteristics

Figure 1 shows a flow chart of patient selection for the two groups. Prior to 31 January 2019, 1562 patients visited our department regularly. Of these, 246 were excluded because of death (infection-related, $n = 3$), prolongation of the interval between visits over 12 weeks (long-term hospitalization due to infection, $n = 2$), or unavailability of follow-up data (moved to another hospital; completed of treatment, mainly in patients with polymyalgia rheumatica; self-suspension of visits). From the middle of 2019 until 31 January 2020, 1584 patients visited our department regularly. Of these, 300 patients were excluded for the same reasons as in 2019. One patient died from infection and 2 patients were excluded due to long term hospitalization for infection in 2020. Accordingly, 1316 patients in Group 2019 and 1284 patients in Group 2020 were included in subsequent analyses. There were 1118 patients who belonged to both groups.

Baseline characteristics of the patients

Table 1 lists the baseline patient characteristics. Median age was 66 years in Group 2019 and 67 years in Group 2020. In univariate analysis, no statistically significant difference was found in terms of underlying autoimmune disease or respiratory comorbidities (30.4% in Group 2019 vs. 32.0% in Group 2020), use of corticosteroids (42.2% vs. 44.3%), Janus kinase (JAK) inhibitors (5.7% and 7.1%), biologic agents (25.5% vs. 26.5%), methotrexate (MTX) (33.0% vs. 33.5%), or other immunosuppressive agent (34.0% vs. 37.0%) such as

tacrolimus, cyclophosphamide, or cyclosporine. There was a greater tendency for immunomodulating agents such as salazosulfapyridine (SASP), iguratimod (IGU), and hydroxychloroquine (HCQ) to be used in Group 2020 (33.1% vs. 39.7%, $p<.001$). The proportion of patients who have not been treated with any immunosuppressive/immunomodulating agent (displayed “no special agent use” in Table 1) was smaller in Group 2020 (6.5% vs. 4.7%, $p=.04$), as they tended to want to prolong their interval of visits and be excluded from the study (data not shown).

Infectious complications

Table 2 shows the comparison of infectious complications between the groups. The proportion of patients with infection was 21.9% in Group 2019 vs. 16.2% in Group 2020 ($p<.001$). The total number of infections per 100 person-years was 28.0 in Group 2019 vs. 19.4 in Group 2020 ($p<.001$). Influenza, pneumonia, other respiratory tract infection, and non-viral dermatological infection showed a significant decrease in 2020 compared with 2019. There was no significant difference between the groups with respect to infection related varicella zoster virus, herpes simplex virus, or gastrointestinal tract, urinary tract, or otolaryngological infection. None of the included patients was infected with SARS-CoV-2 during the observation period of the study.

Figure 2 shows the percentage of infectious complications per month. No cases of influenza were recorded after February 2020.

Binomial logistic regression analyses performed to evaluate the influence of differences in treatment in the groups revealed use of corticosteroids, use of JAK inhibitor, and respiratory comorbidities had high odds ratio for infection in both groups. The use of immunomodulating agents was related to low odds ratio for infection only in Group 2020 (Figure 3).

Vigilance against the COVID-19 pandemic

Of the 1177 patients who visited our outpatient department between 1 April 2020 and 30 June 2020, 1175 completed the questionnaire about change in lifestyle (response rate, 99.8%). As shown in Figure 4, 26% of the patients wore a mask in a crowd before the COVID-19 pandemic, and 70.6% were more careful about wearing masks during the pandemic. Similarly, 12.9% of patients used hand sanitizer on a daily basis before the pandemic, and 80.7% began it during the pandemic. Compliance in these measures ranged from 65.1% (Regular temperature measurement) to 96.6% (Wear a mask in crowds).

Discussion

This study evaluated the frequency of respiratory and dermatological infectious complications in outpatients with autoimmune diseases before and during the COVID-19 pandemic and found that the number of these complications decreased after the start of the pandemic in 2020.

We consider that the COVID-19 pandemic has affected the frequency of infectious diseases in two possible ways. First, measures taken against COVID-19 possibly prevented other infections, especially those transmitted by person-to-person contact. Previous RCTs and meta-analyses have demonstrated that infection-prevention behaviors such as wearing masks [3] and good hand hygiene [2, 4, 6–9] might reduce infections such as diarrhea, upper respiratory infections, influenza, and fever. Regarding social distancing, a comparison of mortality in Philadelphia and St. Louis in 1918 suggested that state-wide social distancing efforts controlled the influenza pandemic [27]. The relationship between social distancing by telework, as a measure against COVID-19, and a reduction of incidence of fever in young employees in 2020 in Japan has been shown [28]. In a large register-based study, Kuitunen et al. reported a decrease in pediatric emergency room visits for respiratory tract infection after lockdown in Finland [12]. The decrease in respiratory infections in the present study is consistent with the findings of these reports.

Regarding other types of infection, there are few reports of any prevention methods for cellulitis other than antibiotics [29]. Although we could not find any studies regarding the effect of hand hygiene on cellulitis, it seems reasonable that good hand hygiene would reduce infection in scratched skin. Gastrointestinal infections would also be expected to decrease with improvements in hand hygiene but showed no decrease in our study. As far as we can tell, two cases of parasite infection (campylobacter and diarrhea after eating raw oysters) were included this survey, but there may have been more infections that are unpreventable by good individual hand hygiene. The measures that restrict close person-person contact may be ineffective for preventing endogenous pathogen-derived infections such as herpes zoster and urinary tract infections.

Second, the possibility of virus-virus interactions on SARS-CoV-2 cannot be ignored. Nickbakhsh et al. showed negative interactions between influenza and non-influenza viruses and positive interactions among non-influenza viruses with real time RT-PCR assays in patients with respiratory infections [30]. Influenza A virus and human coronaviruses (229E, NL63, HKU1) had positive interactions, although uncorrected, in their 2005–2013 survey. Nowak et al. reported that in COVID-19, SARS-CoV-2 positive patients by real-time RT-PCR tended to be negative for other pathogens such as influenza and rhinovirus/enterovirus [31]. Conversely, Kim et al. reported no significant difference in SARS-CoV-2 positivity in groups that were positive/negative for

other respiratory pathogens [32]. The way SARS-CoV-2 interferes with other pathogens has not yet been elucidated and its influence is controversial.

The baseline characteristics in this study were not balanced in terms of the use of immunomodulating agents. Even restricted to 1118 patients common to 2019 and 2020, the use of immunomodulators was increased in 2020 (33.9% vs. 38.5%, $p=.025$, data not shown). A low odds ratio of immunomodulators for infection in Group 2020 was also detected. The total infection rate was 22.3% in 2019 and 16.6% in 2020 ($p<.001$, data not shown). The change in the members from Group 2019 to Group 2020 did not affect the results. As shown in Table 1, the use of HCQ, SASP, and IGU increased in 2020. HCQ is increasingly being recommended for the treatment of systemic lupus erythematosus [33]. The Ministry of Health, Labor and Welfare for Japan and Japan college of rheumatology have published new guidelines for the management of systemic lupus erythematosus in November 2019, which recommended the use of HCQ more strongly than in earlier guidelines. In our clinic, SASP or IGU tended to be added-on in patients with rheumatoid arthritis in whom control was insufficient even after treatment with biologics or JAK inhibitors and who were intolerant of more potent immunosuppressive therapy. Additionally, SASP or IGU have been started in patients who needed to reduce MTX or other immunosuppressive agents for reasons such as renal dysfunction, onset of lung disease, and diagnosis of malignant disease. Owing to their high retention rates, the use of SASP and IGU increased from 2019 to 2020. There might be an effect of sparing dosage of MTX, corticosteroids, or other immunosuppressive agents, which may have decreased the infection rate in 2020. In addition, some reports have suggested the possibility that HCQ or SASP might themselves act protectively against infection, although the mechanism has not been elucidated [34, 35]. The possibility that the imbalance in immunomodulating agents affected our results cannot be excluded.

Several additional limitations of our findings should be considered. The number of some infectious complications may have been too small to enable detection of significance due to the single-center design of the study. We may have missed mild infections because the medical records were managed for the treatment of autoimmune diseases in a specialized clinic, rather than for a survey of infections. Patients might have wanted to avoid visiting a hospital during the COVID-19 pandemic, and therefore infections that improved within a few days might not have been picked up. Because pneumonia, bronchitis, other respiratory tract infections, and cellulitis have lasting symptoms that needed treatment in both of the study years, we consider that there would be few missed infections in such patients. In addition, we were unable to consider all factors that can be associated with infectious complications, such as diabetes mellitus [34, 36], dysphagia [37], complications of malignancy [38], undernutrition [39], leucopenia [36], prophylactic use of sulfamethoxazole/trimethoprim [40], alcoholism

[36], disease duration [41], activities of daily life [42], and the severity of underlying autoimmune diseases [36, 43]. Although corticosteroid dosage is known to be a risk factor for infection [39, 41], it could not be taken into account in our study as the dosage varied during the observation period in most patients.

In conclusion, this study demonstrated that in outpatients with autoimmune diseases, there was a decrease in respiratory and dermatological infectious complications and influenza during the COVID-19 pandemic compared with before the COVID-19 pandemic. The decrease might have resulted from lifestyle changes or from virus-virus interactions with COVID-19, although many other factors, such as changes in treatment trends, should be investigated further. These findings provide new information relevant to infection control for patients in an immunosuppressive state.

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Conflict of interest None.

Authors' contributions

YO conceived the study, collected and handled the data, created the questionnaire, planned and conducted statistical analyses, and drafted the manuscript. YO, TK, MT, YS, TTa and TTs conducted the clinical consultations with the patients and collected the data. JK planned the statistical analyses and contributed to drafting the manuscript. All authors contributed to the discussion, critically reviewed the manuscript, and have given final approval for publication.

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Legends

Figure 1. Flow chart of patient selection.

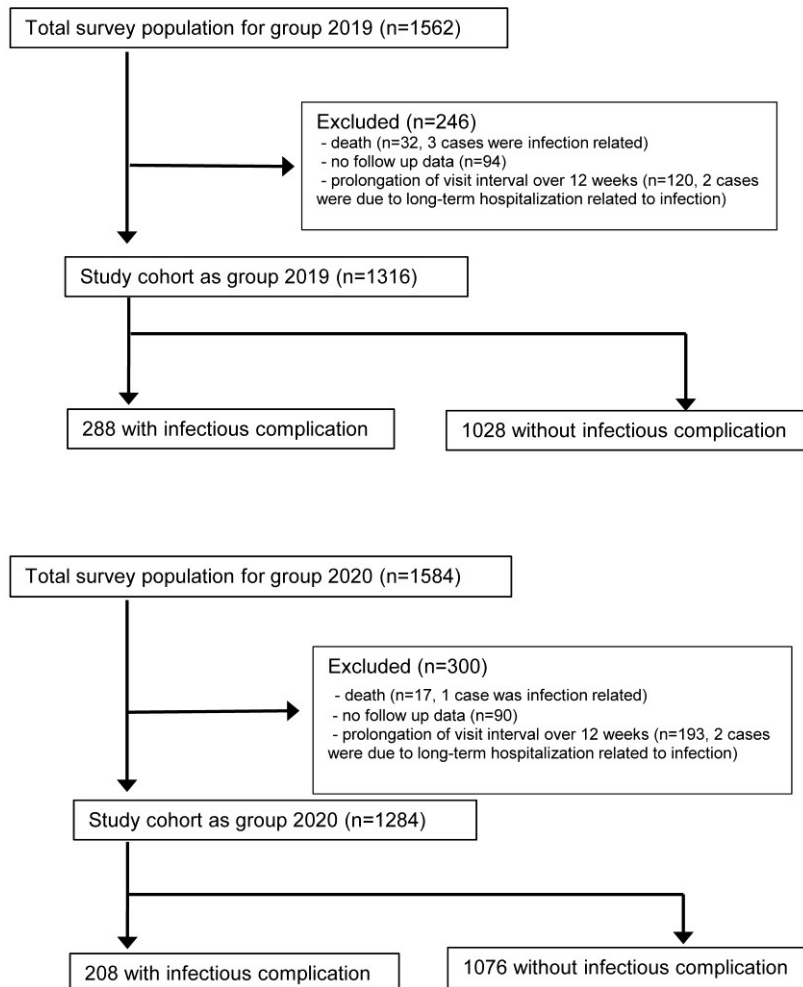


Table 1. Comparison of baseline patient characteristics between the two groups.

Values that do not conform to the normal distribution are expressed as the median (IQR: interquartile range).

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PMR: polymyalgia rheumatica; MCTD: mixed connective tissue disease; PM/DM: polymyositis/dermatomyositis; PsA: psoriatic arthritis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatous polyangiitis; IgG4-RD: IgG4-related disease; AOST: adult-onset Still's disease; AS: ankylosing spondylitis; RSSSPE: remitting seronegative symmetrical synovitis with pitting edema; PN: polyarteritis nodosa. JAK inhibitor: Janus kinase inhibitor; MTX: methotrexate; IVIG: intravenous immunoglobulin.

^aOthers include aortitis, granulomatosis with polyangiitis, antiphospholipid syndrome, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, Castleman's disease, relapsing polychondritis, fibromyalgia, autoinflammatory syndrome, familial mediterranean fever, pachydermoperiostosis, interstitial pneumonia without any other autoimmune disease criteria, gout, undifferentiated arthritis, eosinophilia, and follow-up of positivity of autoantibodies.

^bRespiratory comorbidity includes interstitial pneumonia, organizing pneumonia, lung fibrosis, bronchial asthma, bronchiectasis, emphysema, lung tumor (including post operation), old tuberculosis, and chronic non-tuberculous mycobacteriosis.

^cBiologics includes infliximab, etanercept, adalimumab, tocilizumab, sarilumab, certolizumab pegol, golimumab, abatacept, mepolizumab, and rituximab.

^dOther immunosuppressive agents includes tacrolimus, cyclophosphamide, cyclosporine, azathioprine, mizoribine, and mycophenolate mofetil.

^eImmunomodulators includes salazosulfapyridine, hydroxy chloroquine, bucillamine, iguratimod, colchicine, and gold.

^fNo special agent use means treatment without agents listed above. Patients may have received other agents such as non-steroidal anti-inflammatory agents, anticoagulants, and vasodilators.

*A two-tailed $p < .05$ was considered statistically significant.

Table 2. Comparison of infectious complications between the two groups

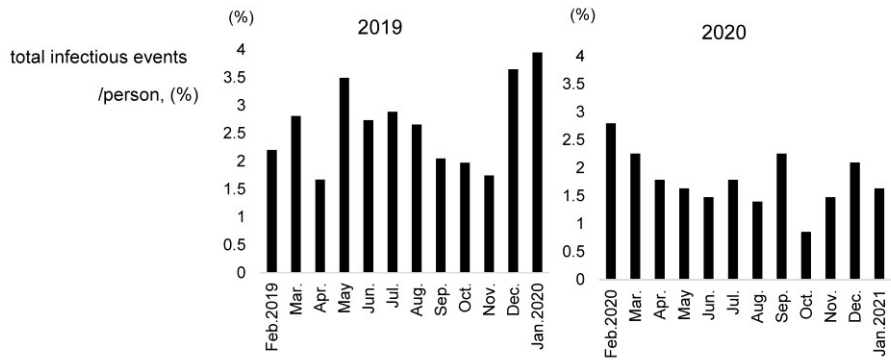
^aOther respiratory tract infections include bronchitis (52 cases in Group 2019 vs. 24 cases in Group 2020), empyema (1 vs. 0), pleural effusion that improved with antibiotics (1 vs. 0), and non-tuberculous mycobacterium infection (1 vs. 4).

^bNon-viral dermatological infections include cellulitis (20 vs. 7), post-traumatic infections, some of which were related to foot deformity (16 vs. 10), infection of pores (5 vs. 4), abscess around the nail (4 vs. 2), and unexplained infection (5 vs. 4). *A two-tailed $p < .05$ was considered statistically significant.

Figure 2. Percentage of infectious complications per month in each group. (a) Incidence rates for the total of infectious events. (b) Incidence rate according to classification. Other respiratory infections included bronchitis, empyema, pleural effusion that improved with antibiotics, and non-tuberculous mycobacterium infection. Non-viral dermatological infections included cellulitis, post-traumatic infection, infection of pores, abscess around the nail, and unexplained infection.

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(a)



(b)

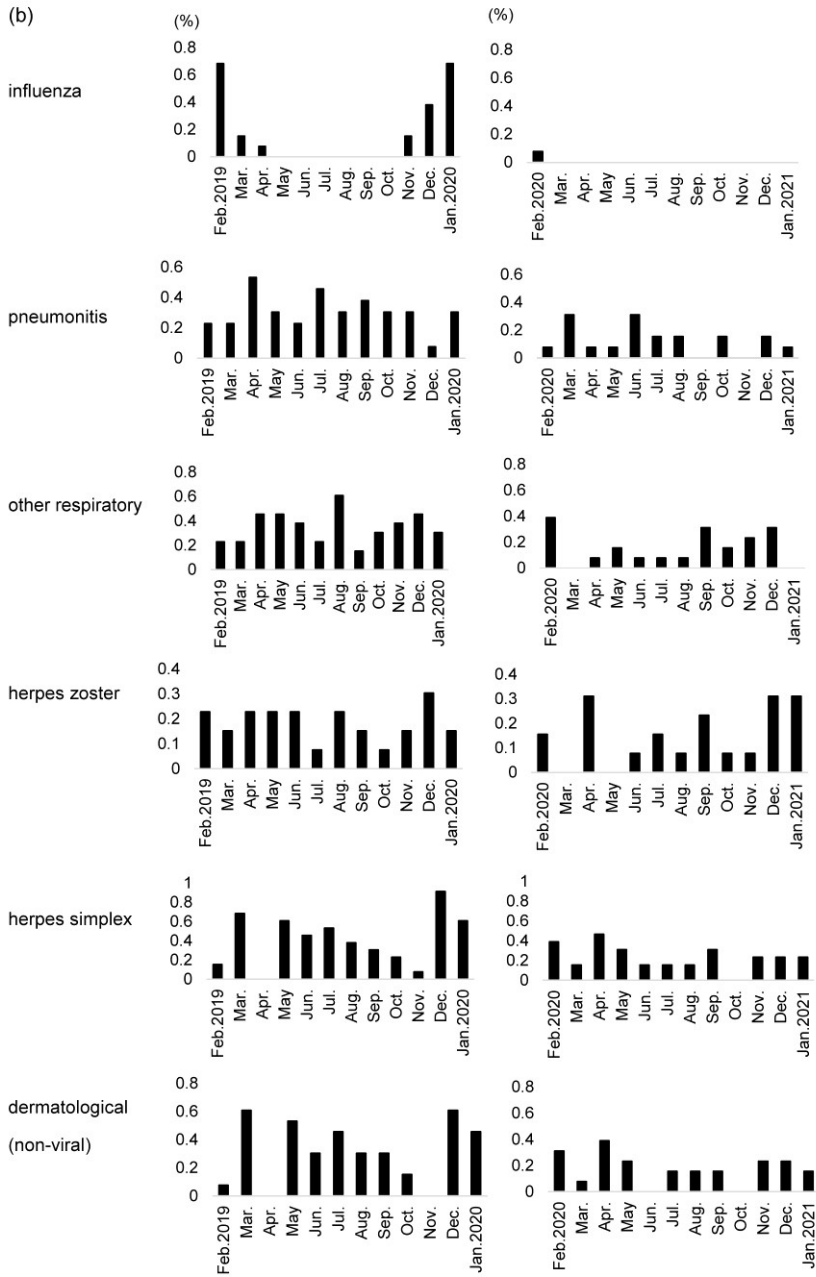
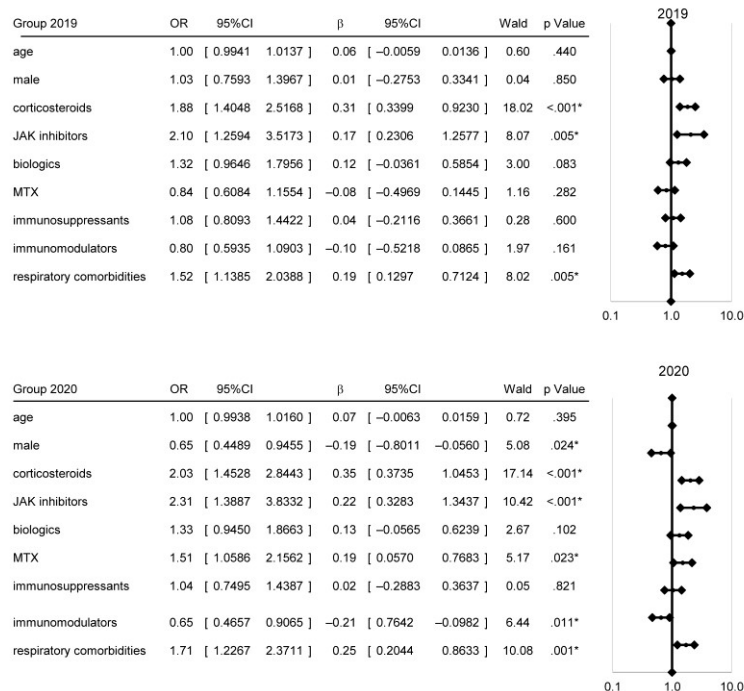


Figure 3. Binomial logistic regression analyses using an episode of infection as an event.

OR: odds ratio; 95%CI: 95% confidence interval; β : standardized partial regression coefficient; Wald: Wald test of partial regression coefficient. *A two-tailed $p < .05$ was considered statistically significant.



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Figure 4. Questionnaire results.

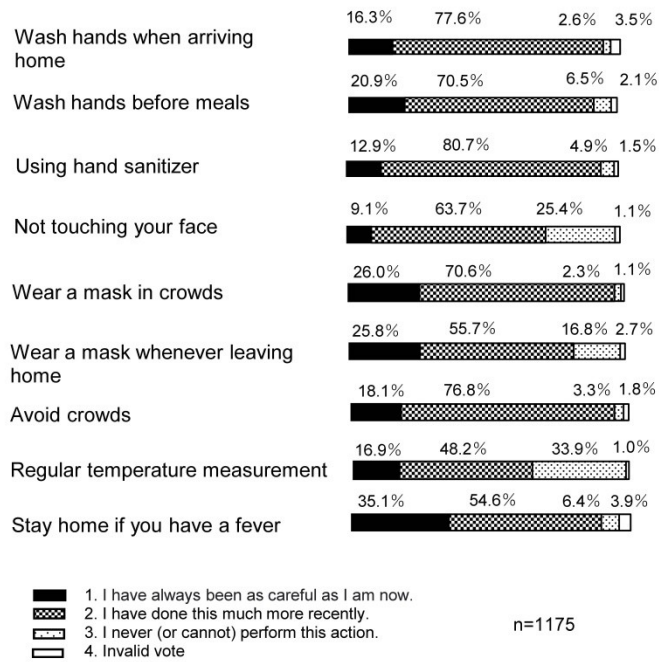


Table 1			
	Group 2019	Group 2020	
	(n=1316)	(n=1284)	p value
Median age, years (IQR)	66 (57–75)	67 (55–75)	
Male, n (%)	346 (26.3)	339 (26.3)	
Diagnosis, n(%)			
RA	842 (64.0)	814 (63.4)	.76
SLE	126 (9.6)	127 (9.9)	.79
Sjogren syndrome	52 (4.0)	51 (4.0)	.98
PMR	43 (3.3)	49 (3.8)	.45
MCTD	43 (3.3)	41 (3.2)	.91
systemic sclerosis	39 (3.0)	36 (2.8)	.81
PM/DM	36 (2.7)	46 (3.6)	.22
PsA	23 (1.7)	18 (1.4)	.48
MPA	21 (1.6)	19 (1.5)	.81
Behcet's disease	17 (1.3)	15 (1.2)	.78
EGPA	17 (1.3)	23 (1.8)	.30
IgG4-RD	13 (1.0)	10 (0.8)	.57
AOSD	12 (0.9)	15 (1.2)	.52
AS	10 (0.8)	7 (0.5)	.50
RSSSPE	10 (0.8)	6 (0.5)	.34
Raynaud syndrome	9 (0.7)	9 (0.7)	.96
PN	7 (0.5)	9 (0.7)	.58
others ^a	61	64	
Respiratory comorbidities ^b , n (%)	400 (30.4)	411 (32.0)	.37
Treatment, n (%)			
corticosteroid use	555 (42.2)	569 (44.3)	.27
JAK inhibitor use	77 (5.7)	92 (7.1)	.17
biologics ^c use	335 (25.5)	340 (26.5)	.55
MTX use	434 (33.0)	430 (33.5)	.78
other immunosuppressant ^d use	447 (34.0)	475 (37.0)	.11
immunomodulator ^e use	435 (33.1)	510 (39.7)	<.001*
salazosulfapyridine	324 (24.6)	370 (28.8)	.02*

bucillamine	61 (4.6)	69 (5.4)	.23
igratimod	45 (3.4)	72 (5.6)	.01*
hydroxychloroquine	28 (2.1)	44 (3.4)	.04*
no special agent use ^f	86 (6.5)	60 (4.7)	.04*
IVIG use	2 (0.2)	2 (0.2)	
cancer chemotherapy	1 (0.1)	2 (0.2)	

Table 2			
	group 2019	group 2020	
	(n=1316)	(n=1284)	pValue
number of patients with infections, n (%)	288 (21.9)	208 (16.2)	<.001*
total number of infections, n (/100 person-years)	369 (28.0)	249 (19.4)	<.001*
event, n (/100 person-years)			
respiratory tract infection	131 (10.0)	45 (3.5)	<.001*
influenza	28 (2.1)	1 (0.1)	<.001*
pneumonia	48 (3.6)	20 (1.6)	<.001*
other ^a	55 (4.2)	24 (1.9)	<.001*
dermatological infection	94 (7.1)	59 (4.6)	.006*
herpes zoster	29 (2.2)	23 (1.8)	.45
herpes simplex	15 (1.1)	9 (0.7)	.24
non-viral ^b	50 (3.8)	27 (2.1)	.001*
Urological infection	44 (3.3)	49 (3.8)	.52
gastrointestinal infection	38 (2.9)	38 (3.0)	.91
diarrhea and/or vomiting	33 (2.5)	29 (2.2)	.68
appendicitis, diverticulitis, or gallstone cholecystitis	5 (0.4)	9 (0.7)	.26
otolaryngological infection (otitis media, sinusitis, etc.)	28 (2.1)	27 (2.1)	.96
dental infection	14 (1.1)	13 (1.0)	.95
other	20 (1.5)	18 (1.4)	