Post-COVID condition in patients with inflammatory rheumatic diseases

Post-COVID condition in patients with inflammatory rheumatic diseases: a prospective cohort study in the Netherlands

Laura Boekel, Sadaf Atiqi, Maureen Leeuw, Femke Hooijberg, Yaëlle R. Besten, Rosa Wartena, Maurice Steenhuis, Erik Vogelzang, Casper Webers, Annelies Boonen, Martijn Gerritsen, Willem F Lems, Sander W Tas, Ronald F van Vollenhoven, Alexandre E Voskuyl, Irene van der Horst-Bruinsma, Mike Nurmohamed, Theo Rispens, Gertjan Wolbink

Summary

Background Studies on long-term consequences of COVID-19, commonly referred to as post-COVID condition, in patients with inflammatory rheumatic diseases are scarce and inconclusive. Furthermore, classifying patients with inflammatory rheumatic diseases as having post-COVID condition is complicated because of overlapping symptoms. Therefore, we investigated the risk of post-COVID condition and time until recovery, and compared the prevalence of symptoms seen in post-COVID condition, between patients with inflammatory rheumatic diseases and healthy controls, with and without a history of COVID-19.

Methods In this substudy we used data from an ongoing prospective cohort study in the Netherlands. All adult patients with inflammatory rheumatic diseases from the Amsterdam Rheumatology and Immunology Center in Amsterdam, the Netherlands, were invited to participate in the study between April 26, 2020, and March 1, 2021. All patients were asked, but not obliged, to recruit their own control participant of the same sex, of comparable age (< 5 years), and without an inflammatory rheumatic disease. Demographic and clinical data, including data on the occurrence of SARS-CoV-2 infections, were collected via online questionnaires. On March 10, 2022, all study participants received a questionnaire on the occurrence, onset, severity, and duration of persistent symptoms during the first 2 years of the COVID-19 pandemic, independent of their history of SARS-CoV-2 infection. Additionally, we prospectively monitored a subset of participants who had a PCR or antigen confirmed SARS-CoV-2 infection in the 2-month period surrounding the questionnaire in order to assess COVID-19 sequelae. In line with WHO guidelines, post-COVID condition was defined as persistent symptoms that lasted at least 8 weeks, started after the onset and within 3 months of a PCR or antigen-confirmed SARS-CoV-2 infection, and could not be explained by an alternative diagnosis. Statistical analyses included descriptive statistics, logistic regression analyses, logistic-based causal mediation analyses, and Kaplan-Meier survival analyses for time until recovery from post-COVID condition. In exploratory analyses, E-values were calculated to investigate unmeasured confounding.

Findings A total of 1974 patients with inflammatory rheumatic disease (1268 [64%] women and 706 [36%] men; mean age 59 years [SD 13]) and 733 healthy controls (495 [68%] women and 238 [32%] men; mean age 59 years [12]) participated. 468 (24%) of 1974 patients with inflammatory rheumatic disease and 218 (30%) of 733 healthy controls had a recent SARS-CoV-2 omicron infection. Of those, 365 (78%) of 468 patients with inflammatory rheumatic disease and 172 (79%) of 218 healthy controls completed the prospective follow-up COVID-19 sequelae questionnaires. More patients than controls fulfilled post-COVID condition criteria: 77 (21%) of 365 versus 23 (13%) of 172 (odds ratio [OR] 1·73 [95% CI 1·04–2·87]; p=0·033). The OR was attenuated after adjusting for potential confounders (adjusted OR 1·53 [95% CI 0·90–2·59]; p=0·12). Among those without a history of COVID-19, patients with inflammatory diseases were more likely to report persistent symptoms consistent with post-COVID condition than were healthy controls (OR 2·52 [95% CI 1·92–3·32]; p<0·0001). This OR exceeded the calculated E-values of 1·74 and 1·96. Recovery time from post-COVID condition was similar for patients and controls (p=0·17). Fatigue and loss of fitness were the most frequently reported symptoms in both patients with inflammatory rheumatic disease and healthy controls with post-COVID condition.

Interpretation Post-COVID condition after SARS-CoV-2 omicron infections was higher in patients with inflammatory rheumatic disease than in healthy controls based on WHO classification guidelines. However, because more patients with inflammatory rheumatic disease than healthy controls without a history of COVID-19 reported symptoms that are commonly used to define a post-COVID condition during the first 2 years of the pandemic, it is likely that the observed difference in post-COVID condition between patients and controls might in part be explained by clinical manifestations in the context of underlying rheumatic diseases. This highlights the limitations of applying current criteria for post-COVID condition in patients with inflammatory rheumatic disease, and suggests it might be appropriate for physicians to keep a nuanced attitude when communicating the long-term consequences of COVID-19.

Lancet Rheumatol 2023; 5: e375–85

Published Online May 31, 2023 https://doi.org/10.1016/S2665-9913(23)00127-3

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Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Reade (L Boekel BSc, S Atiqi MD, M Leeuw MSc, F Hooijberg MD, Y R Besten BSc, R Wartena BSc, M Gerritsen PhD, Prof W F Lems MD, Prof M Nurmohamed MD, G Wolbink PhD), **Department of Rheumatology and Clinical Immunology, Amsterdam Rheumatology and Immunology Center, VU University Medical Center** (Prof W F Lems, Prof A E Voskuyl PhD, Prof M Nurmohamed), **Department of Rheumatology and Clinical Immunology, Amsterdam Rheumatology and Immunology Center, University of Amsterdam** (Prof S W Tas MD, Prof R F van Vollenhoven MD), **Department of Immunopathology, Sanquin Research and Landsteiner Laboratory** (M Steenhuis PhD, T Rispens PhD, G Wolbink), **and Department of Medical Microbiology and Infection Control** (E Vogelzang PhD), **Amsterdam University Medical Center, Amsterdam, Netherlands; Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands** (C Webers PhD, Prof A Boonen PhD); **Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, Netherlands** (C Webers, Prof A Boonen); **Department of Rheumatic Diseases, Radboud, University Medical Center,**

Nijmegen, Netherlands
(Prof I van der Horst-Bruinsma MD)
Correspondence to:
Laura Boekel, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Reade, Amsterdam University Medical Center, 1056 AB, Amsterdam, Netherlands
l.boekel@reade.nl

Funding ZonMw (the Netherlands organization for Health Research and Development) and Reade foundation.

Introduction

Effects of inflammatory rheumatic diseases and treatment with immunosuppressive agents on the acute infection phase of SARS-CoV-2 have been extensively investigated, but there is still a paucity of data on long-term consequences of SARS-CoV-2 infection. Long-term consequences of COVID-19 are commonly referred to as post-COVID condition (also known as long COVID), and are currently seen as conditions that might affect a substantial proportion of the general population.[1,2] However, post-COVID condition is still poorly defined; it can include any subjective symptom persisting beyond the acute infection phase of SARS-CoV-2, if other possible causes can be ruled out.[3] A large amount of heterogeneity exists among studies that have investigated post-COVID condition, and findings of epidemiological studies are still largely inconclusive. Pathophysiological mechanisms underlying post-COVID condition also remain incompletely understood, although recent studies suggest that persistent inflammation after the acute infection phase and auto-immune reactions might play a crucial role in its development.[4] The presence of underlying rheumatic diseases that are characterised by chronic inflammation and immune dysregulation might therefore increase the risk of post-COVID condition or affect the clinical presentation and severity.[5] However, whether patients with inflammatory rheumatic diseases are more susceptible to post-COVID condition, and whether the clinical phenotype differs from people in the general population, remains unclear. Additionally, studies have not yet investigated whether correctly classifying patients with inflammatory rheumatic diseases as having post-COVID condition cases is complicated by increased background noise; for example, pre-existing symptoms or new symptoms that are not caused by post-COVID conditions (eg, caused by the underlying rheumatic disease). Epidemiological studies investigating these research questions might contribute to understanding post-COVID condition and help rheumatologists to inform and guide their patients during the ongoing COVID-19 pandemic. Therefore, we aimed to compare the incidence and characteristics of post-COVID condition in patients with inflammatory rheumatic diseases and healthy controls during the period when the omicron variant (BA.1 and BA.2 lineages) was dominant, as part of a large prospective COVID-19 focused cohort study, while accounting for shared symptoms between post-COVID condition and inflammatory rheumatic diseases.

Methods

Study design and participants

In this study, we collected data from participants enrolled in a Dutch prospective cohort study that was designed to

Research in context

Evidence before this study

We searched PubMed and Google Scholar on March 8, 2023, for studies published in English since Jan 1, 2020, that describe long-term consequences of COVID-19 in patients with inflammatory rheumatic diseases. Long-term consequences are commonly referred to as post-COVID condition or long-COVID and could affect a substantial proportion of the population. However, post-COVID conditions are still poorly defined, and pathophysiological mechanisms underlying post-COVID condition remain incompletely understood. Hence, it is still unknown whether patients with inflammatory rheumatic diseases are more susceptible to post-COVID condition and whether the clinical phenotype differs from people from the general population.

Added value of this study

To our knowledge, this is the first prospective study to compare long-term consequences of COVID-19 between patients with rheumatic inflammatory diseases and healthy controls. A unique aspect of this study is that participants were enrolled before infection with SARS-CoV-2, which minimises the risk of selection bias. Additionally, we addressed and quantified systematic differences in the reporting of persistent symptoms used to define post-COVID condition between patients and controls. This is relevant because overlap in the clinical picture of post-COVID condition and inflammatory rheumatic diseases could complicate the correct identification of post-COVID condition in patients with inflammatory rheumatic diseases, and thus bias comparisons with healthy controls. We found that more patients with inflammatory rheumatic diseases than healthy controls developed post-COVID condition when we applied WHO criteria, but symptomology and time to recovery from post-COVID condition were similar between the groups. Furthermore, we observed that patients with inflammatory rheumatic diseases without a history of COVID-19 were more likely to report persistent symptoms that are used to identify post-COVID condition than were healthy controls.

Implications of all the available evidence

Our data emphasise the limitations of applying current WHO criteria of post-COVID condition in patients with inflammatory rheumatic diseases, which implies that studies on this topic should be interpreted with caution. Additionally, we believe it might be appropriate for rheumatologists to have a nuanced attitude when communicating information regarding long-term consequences of COVID-19 to their patients.

compare the disease severity of COVID-19 between patients with inflammatory rheumatic diseases and healthy controls (Netherlands Trial Register, trial ID NL 8513). The design of the study has been previously described.[6–9] Briefly, patients aged 18 years and older with inflammatory rheumatic diseases from the Amsterdam Rheumatology and Immunology Center (Amsterdam, Netherlands), were invited to participate in the study between April 26, 2020, and March 1, 2021. All participants were asked (but not obliged) to recruit their own healthy control participant of the same sex, comparable age (difference of <5 years) and without an inflammatory rheumatic disease. The research protocol was approved by the medical ethical committee of the VU University Medical Center (registration number, 2020.169). All participants provided written informed consent.

Procedures

Demographic data were collected at baseline and included age, sex, height, weight, smoking status, autoimmune disease type, and educational level. At baseline and during follow-up, participants reported their disease activity, medication use, and COVID-19-related clinical characteristics. Demographic and clinical data were collected with online questionnaires distributed via email. Sex data were self-reported, participants could choose between "male", "female", and "other". In case of "other", participants could explain their answer in an open text field. The baseline questionnaire was sent to participants when they were included in the study. Until the start of the primary vaccination campaign in the Netherlands (January, 2021), the first and second follow-up questionnaires were sent to participants 1–4 months and 5–9 months after completion of the baseline questionnaire. Following this, questionnaires were then sent to participants at fixed timepoints on April 26, Aug 24, and Dec 10, 2021, and on March 10, 2022. Data collected included vaccination dates, vaccine type, information on COVID-19 symptoms, and admissions to a hospital due to COVID-19. In the questionnaire sent on March 10, 2022, participants were also asked about the occurrence, onset, severity, and duration of a series of one or more pre-defined symptoms characteristic of post-COVID condition during the first 2 years of the COVID-19 pandemic (from Jan 1, 2020, to Dec 31, 2021), independent of their history with SARS-CoV-2 infections (appendix pp 11–12). Additionally, participants of the March 10, 2022 questionnaire with a PCR or antigen-confirmed SARS-CoV-2 infection between Jan 1 and April 25, 2022, a time period that coincided with the omicron dominant period in the Netherlands, were included for prospective monitoring of the occurrence of post-COVID condition and recovery (appendix pp 11–12). These participants received additional questionnaires at fixed timepoints: on June 25 and Sept 20, 2022. The questions were similar to those in the March 10, 2022 questionnaire, except for the obligatory reporting of new onset of symptoms with SARS-CoV-2 infection; participants were specifically asked about new onset symptoms after their SARS-CoV-2 infection. The second questionnaire was only sent to participants whose symptoms had not yet resolved at the time of completing the first questionnaire.

Serum samples were collected multiple times during follow-up for analyses of SARS-CoV-2 antibodies via regular blood sampling at the local research institute or via a finger prick at home.[10,11] Sampels were collected in October, 2020, and January, 2021, after the first SARS-CoV-2 vaccination, after the second SARS-CoV-2 vaccination, and in October–November, 2021. Serum samples that were collected before the first SARS-CoV-2 vaccination were used to identify participants with a history of COVID-19 before vaccination. Shortly before the start of the Dutch COVID-19 vaccination campaign, all participants were invited for blood sampling to cross-sectionally screen the cohort for COVID-19 cases.[7] All pre-vaccination serum samples were analysed for the presence of SARS-CoV-2 specific antibodies with a receptor binding domain antibody bridging ELISA (in house) with a 98·1% sensitivity and a 99·5% specificity.[10,11]

Outcomes

The primary outcome of this study was to compare the risk of post-COVID condition after a SARS-CoV-2 omicron infection between patients with inflammatory rheumatic diseases and healthy controls, using WHO guidelines for classification of cases with post-COVID condition. The primary outcome was asssessed in all participants with a confrimed SARS-CoV-2 infection during the omicron-dominant period (Jan 1–April 25, 2022), with available follow-up data after the infection. A SARS-CoV-2 omicron infection was defined as a self-reported positive SARS-CoV-2 antigen or PCR test. SARS-CoV-2 infections after Jan 1, 2022, were assumed to be due to the omicron variant, because it was the dominant variant during the study period in the Netherlands. In line with WHO guidelines,[3] participants with post-COVID condition were defined as those who reported any symptom that lasted at least 8 weeks, started after the onset and within 3 months of a PCR or antigen-confirmed SARS-CoV-2 infection, and could not be explained by an alternative diagnosis. Secondary objectives were to compare disease characteristics of post-COVID condition, recovery from post-COVID condition (defined as time to complete resolution of symptoms), and health-care utilisation after SARS-CoV-2 omicron infections between patients with inflammatory rheumatic diseases and healthy controls. As a further secondary outcome, we aimed to investigate whether correctly classifying patients with inflammatory rheumatic diseases as having post-COVID condition is complicated by the occurrence of persistent symptoms that could be attributed to both post-COVID condition and inflammatory rheumatic disease. To investigate this, we

See Online for appendix

compared the prevalence of persistent symptoms (≥8 weeks) that are observed in post-COVID condition between patients with inflammatory rheumatic disease and healthy controls with and without a history of COVID-19. Participants could select the following symptoms: loss of fitness, shortness of breath, memory problems, concentration problems, depression, cough, chest pain, palpitations, fatigue, sleeping problems, headache, myalgia, increased arthralgia, skin rash, excessive sweating, fever, loss of taste or smell, general malaise, rhinorrhea, and other (a free text box for participants to list symptoms not in the questionnaire).

Statistical analysis

Participants were included for the retrospective study if they completed the questionnaire sent on March 10, 2022. Characteristics of participants are presented as mean (SD), median (IQR), or frequencies and proportions, depending on the type and distribution of the data. Analyses on post-COVID condition after SARS-CoV-2 omicron infections only included participants who were prospectively monitored after a SARS-CoV-2 omicron infection and completed the first COVID-19 sequelae questionnaire (sent on June 25, 2022).

Univariable and multivariable logistic regression analyses were used to compare the risk of developing post-COVID condition after a SARS-CoV-2 omicron infection between patients with inflammatory rheumatic disease and healthy controls. Confounding was investigated for age, sex, BMI, cardiovascular disease, diabetes, chronic pulmonary disease, vaccination status, history of COVID-19 before Jan 1, 2022, and disease severity of the acute infection phase of SARS-CoV-2. We hypothesised that disease severity of the acute infection phase of SARS-CoV-2 could be a mediator in the association between participant status (patient with inflammatory rheumatic disease *vs* healthy control) and post-COVID condition (appendix p 9), as it has been demonstrated that disease severity was an important risk factor for post-COVID condition in people with mild COVID-19.[12] We used a regression-based approach for causal mediation analyses to investigate this. Loglinear regression models were used for the outcome variable because the rare-outcome assumption (prevalence <0·10) was violated. Both crude and adjusted direct effects (the effect of participant status on post-COVID condition not mediated through disease severity), indirect effects (the effect of participant status on post-COVID condition mediated through disease severity), and total effects (the combined effect of the direct and indirect effect) were estimated. Adjusted models included age, sex, and presence of comorbidities (obesity; cardiovascular disease; pulmonary disease or diabetes) as covariates. In each model, age was conditioned at 55 years (the median), and the presence of comorbidities was conditioned on absent. For descriptive purposes, models with sex conditioned on males and females were reported separately. There was no determinant-mediator interaction, which meant that the association between participant status and post-COVID condition did not differ for different values of disease severity (WHO COVID-19 severity scores <3 *vs* ≥3) For each model, the proportion mediated, which quantifies the contribution of mediation to the total effect, was calculated once as: pure natural indirect effect/total effect. Exploratory analyses were done to investigate unmeasured confounding. We hypothesised that the occurrence of clinical manifestations that could be attributed to both post-COVID condition and rheumatic diseases can introduce systematic (unmeasured) differences in the reporting of persistent symptoms between patients with inflammatory rheumatic disease and healthy controls, with patients reporting more symptoms than controls. The E-value is an approach to help investigate the robustness of the main study result by calculating the minimum strength that unmeasured confounding must have to negate the association between the exposure and outcome, and evaluating whether that magnitude is plausible.[13] We therefore calculated E-values for the association between participant status and post-COVID condition. Subsequently, we used our retrospective data asking about persistent symptoms during the first 2 years of the COVID-19 pandemic to quantify the difference between patients with inflammatory rheumatic disease and healthy controls. For both patients and healthy controls, three separate models using logistic regression analyses were created: (1) a model including all study participants, (2) participants with a history of COVID-19, and (3) participants who had not yet been infected with SARS-CoV-2 virus before Jan 1, 2022. All models were a priori adjusted for age and sex. If the estimated ORs were similar to the calculated E-values, it would be plausible to assume that systematic differences in the reporting of persistent symptoms could account for differences in post-COVID condition between patients with inflammatory rheumatic disease and healthy controls.

In participants who met WHO criteria for post-COVID condition, Kaplan-Meier survival analyses were used to compare time until recovery from post-COVID condition following a recent SARS-CoV-2 omicron infection between patients with inflammatory rheumatic disease and healthy controls during the first 26 weeks after the onset of infection. The symptomology of post-COVID condition is presented in bar charts.

Descriptive statistics, bar charts, and line graphs were used to compare characteristics of persistent symptoms between patients with inflammatory rheumatic disease and healthy controls with and without a history of COVID-19. P values less than 0·05 were considered statistically significant. SPSS (version 27.0) and R (version 4.0.3) were used for statistical analyses. GraphPad Prism (version 6.0) was used to create the figures.

	Patients with inflammatory rheumatic disease (n=1974)	Healthy controls (n=733)
Patient characteristics		
Age, years	59 (13)	59 (12)
Female	1268 (64%)	495 (68%)
Male	706 (36%)	238 (32%)
BMI, kg/m²	26 (5)	25 (4)
Coexisting conditions		
Cardiovascular disease	256 (13%)	51 (7%)
Chronic pulmonary disease	231 (12%)	43 (6%)
Diabetes	108 (5%)	24 (3%)
Obesity	343(17%)	75 (10%)
Type of rheumatic disease		
Rheumatoid arthritis	1065 (54%)	..
Psoriatic arthritis	306 (16%)	..
Ankylosing spondylitis	276 (14%)	..
Axial or peripheral spondylarthritis	38 (2%)	..
Juvenile idiopathic arthritis	34 (2%)	..
Systemic lupus erythematosus	105 (5%)	..
Vasculitis	40 (2%)	..
Polymyalgia rheumatica	96 (5%)	..
Sjögren's disease	106 (5%)	..
Systemic sclerosis	45 (2%)	..
Mixed connective tissue disease	11 (1%)	..
Gout	79 (4%)	..
Other rheumatic diseases	143 (7%)	..
Immunosuppressants*		
No immunosuppressive medication	390 (20%)	723 (99%)
Conventional synthetic DMARDs	1087 (55%)	4 (1%)
Methotrexate	803 (41%)	2 (<1%)
Hydroxychloroquine	262 (13%)	3 (<1%)
Sulfasalazine	96 (5%)	0
Azathioprine	50 (3%)	0
Biological DMARDs	783 (40%)	0
TNF inhibitor	606 (31%)	0
Anti-CD20 therapy	49 (2%)	0
IL-6 inhibitor	33 (2%)	0
Other immunosuppressants	301 (15%)	5 (1%)
Prednisone	278 (14%)	5 (1%)
SARS-CoV-2 vaccination		
Number of vaccine doses		
None	80 (4%)	30 (4%)
One	18 (1%)	11 (2%)
Two	239 (12%)	117 (16%)
Three	1407 (71%)	524 (71%)
More than three	230 (12%)	51 (7%)
Vaccine type primary vaccination†		
AstraZeneca	358/1869 (19%)	157/694 (23%)
(Table 1 continues in next column)		

	Patients with inflammatory rheumatic disease (n=1974)	Healthy controls (n=733)
(Continued from previous column)		
Pfizer–BioNTech	1238/1869 (66%)	396/694 (57%)
Moderna	206/1869 (11%)	104/694 (15%)
Janssen	36/1869 (2%)	33/694 (5)%
Mix	31/1869 (2%)	4/694 (1%)
SARS-CoV-2 infections		
Before Jan 1, 2022		
Wildtype (alpha) variant	262 (13%)	115 (16%)
Delta variant	93 (5%)	32 (4%)
After Jan 1, 2022 (omicron infection)	468 (24%)	218 (30%)
PCR-confirmed	169/468 (36%)	82/218(38%)
Antigen-confirmed	92/468 (20%)	32/218(15%)
PCR and antigen test confirmed	210/468 (45%)	104/218(48%)

Data are mean (SD), n (%), or n/N (%). DMARD=disease-modifying anti-rheumatic drug. TNF=tumour necrosis factor. IL=interleukin. *Participants could be treated with multiple immunosuppressants. †Vaccine type was unknown for 25 patients with inflammatory rheumatic disease and nine healthy controls.

Table 1: **Characteristics of patients with inflammatory rheumatic disease and healthy controls**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In total, 1974 patients with inflammatory rheumatic disease and 733 healthy controls completed the questionnaire sent on March 10, 2022, and were included in this study. Characteristics of patients with inflammatory rheumatic disease and healthy controls are shown in table 1. Among patients with inflammatory rheumatic disease, mean age was 59 years (SD 13), 1268 (64%) of 1974 were women and 706 (36%) were men; and among healthy controls, mean age was 59 years (SD 12), 495 (68%) of 733 were women and 238 (32%) were men (table 1). Cardiovascular disease, chronic pulmonary disease, diabetes, and obesity were more frequent in patients with inflammatory rheumatic disease than in healthy controls. Rheumatoid arthritis was the most common underlying disease in patients with inflammatory rheumatic disease (1065 [54%] of 1974), and patients were most frequently being treated with methotrexate (803 [41%] of 1974) and tumour necrosis factor inhibitors (606 [31%] of 1974). History of COVID-19 and SARS-CoV-2 vaccination status (number of doses and vaccine type) were similar for patients with inflammatory rheumatic disease and healthy controls.

In total, 365 (78%) of 466 patients with inflammatory rheumatic disease and 172 (79%) of 218 healthy controls with a SARS-CoV-2 omicron infection completed the first

	OR (95% CI)	p value
Prospective data: risk of meeting WHO criteria for post-COVID condition		
Univariable model		
Healthy controls	1 (ref)	..
Patients with rheumatic diseases	1·73 (1·04–2·87)	0·033
E-value*	1·96 (1·16)	..
Multivariable model		
Healthy controls	1 (ref)	..
Patients with rheumatic diseases	1·53 (0·90–2·59)	0·12
Age	1·02 (1·00–1·12)	0·14
Sex		
Male	1 (ref)	..
Female	1·08 (0·65–1·79)	0·78
BMI	1·06 (1·01–1·12)	0·015
Cardiovascular disease	0·86 (0·41–1·84)	0·70
Pulmonary disease	1·13 (0·55–2·33)	0·74
History of COVID-19 before Jan 1, 2022	1·35 (0·72–2·52)	0·35
Vaccination status		
Unvaccinated	1 (ref)	..
Vaccinated	0·88 (0·35–2·21)	0·79
Severity of acute infection phase of SARS-CoV-2†		
WHO severity score <3	1 (ref)	..
WHO severity score ≥3	3·07(1·81–5·22)	<0·0001
E-value*	1·78 (1·00)	..
Retrospective data: risk of reporting persistent symptoms between Jan 1, 2020, and Jan 1, 2022		
All participants‡		
Healthy controls	1 (ref)	..
Patients with rheumatic diseases	2·11 (1·69 – 2·64)	<0·0001
Participants with a history of COVID-19‡		
Healthy controls	1 (ref)	..
Patients with rheumatic diseases	1·62 (1·08–2·45)	0·021
Participants without a history of COVID-19‡		
Healthy controls	1 (ref)	..
Patients with rheumatic diseases	2·52 (1·92–3·32)	<0·0001

Results of logistic regression analyses and E-value analyses for the unadjusted and adjusted association between participant status and post-COVID condition. Data are OR (95% CI), and point estimates and the lower limit of the 95% CI for E-values, unless otherwise specified. The prospective analyses included all participants who were prospectively monitored after a SARS-CoV-2 omicron infection and completed the first COVID-19 sequelae questionnaire. The retrospective analyses included all participants who completed the questionnaire sent on March 10, 2022. p<0·05 was considered statistically significant. OR=odds ratio. *Data are E-value for point estimate and the lower limit of the confidence interval from left to right. †A WHO score of 1 indicates asymptomatic infection, a score of 2 indicates mild disease without the need for assistance, a score of 3 indicates mild disease with need for assistance (ie, could not care for themselves in daily life due to the severity of their symptoms) but no hospital admission, a score of 4 or higher indicates admission to hospital, intensive care unit, or death. ‡Models were adjusted for age and sex.

Table 2: **Logistic regression and E-value analyses**

COVID-19 sequelae questionnaire (appendix p 6). Participants who did not complete the questionnaire were slightly younger than those who completed the questionnaire (appendix p 5). 77 (21%) of 365 patients with inflammatory rheumatic disease and 23 (13%) of 172 healthy controls had post-COVID condition according to WHO classification criteria. Unadjusted logistic regression analyses showed that having a rheumatic disease was associated with higher odds of post-COVID condition (OR 1·73 [95% CI 1·04– 2·87], p=0·033; table 2). After adjusting for confounding, the association no longer reached statistical significance (adjusted [a] OR 1·53 [95% CI 0·90–2·59], p=0·12). Post-hoc evaluation of covariables in the regression model showed that higher BMI (aOR 1·06 [95% CI 1·01–1·12]; p=0·015) and an increased disease severity of the acute infection phase of SARS-CoV-2 (aOR 3·07 [1·81–5·22]; p<0·0001) were associated with higher odds of post-COVID condition (table 2). Mediation analyses showed that the proportion of the association between participant status and post-COVID condition mediated by disease severity of acute infection phase of SARS-CoV-2 was low (17·1% for the crude analysis, 17·6% for the first adjusted analysis, and 11·7% for the second adjusted analysis), which corresponds with the low odds of indirect effects (OR range, 1·05–1·08; table 3).

The baseline characteristics were similar for patients with inflammatory rheumatic disease and healthy controls with and without post-COVID condition (appendix p 2). As expected, patients with inflammatory rheumatic disease and healthy controls with post-COVID condition more frequently had WHO COVID-19 severity scores 3 compared to those without post-COVID condition; 26 (34%) of 77 patients with inflammatory rheumatic disease and six (26%) of 23 healthy controls with post-COVID condition compared with 44 (15%) of 288 patients with inflammatory rheumatic disease and 14 (9%) of 149 healthy controls without post-COVID condition (appendix p 2). Fatigue and loss of fitness were the most frequently reported symptoms in both patients with inflammatory rheumatic disease and healthy controls with post-COVID condition (appendix p 7). Clustering of the four most frequently reported symptoms is shown in figure 1. Time to recovery from post-COVID condition was similar for patients with inflammatory rheumatic disease and healthy controls (figure 2; p=0·17).

More patients with inflammatory rheumatic disease than healthy controls with post-COVID condition reported contacting a health-care professional because of persistent symptoms after a SARS-CoV-2 infection (40 [52%] of 77 patients *vs* seven [30%] of 23 healthy controls; appendix p 3). Patients with inflammatory rheumatic disease most frequently contacted a general practitioner (29 [73%] of 40), a rheumatologist (14 [35%] of 40), or physiotherapist (14 [35%] of 40); 20 (26%) of 77 patients with inflammatory rheumatic disease had contact with multiple health-care professionals. By contrast, healthy controls exclusively contacted a general practitioner (appendix p 3). 25 (63%) of 40 patients with inflammatory rheumatic disease and four (57%) of seven

	Crude		Adjusted*		Adjusted†	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Total effects						
Healthy controls	1 (ref)	..	1 (ref)	..	1 (ref)	..
Patients with inflammatory rheumatic disease	1·58 (1·03–2·42)	0·037	1·50 (0·98–2·30)	0·063	1·46 (0·95–2·23)	0·081
Direct effects						
Healthy controls	1 (ref)	..	1 (ref)	..	1 (ref)	..
Patients with inflammatory rheumatic disease	1·46 (0·95–2·24)	0·082	1·40 (0·91–2·13)	0·12	1·40 (0·91–2·13)	0·12
Indirect effects						
Healthy controls	1 (ref)	..	1 (ref)	..	1 (ref)	..
Patients with inflammatory rheumatic disease	1·08 (1·00–1·17)	0·054	1·07 (0·99–1·16)	0·085	1·05 (0·99–1·10)	0·099

Results of regression-based approach for causal mediation analyses using a log-linear model for the outcome variable. p<0·05 was considered statistically significant.
*Covariates are conditioned on age, 55 years; sex, female; comorbidities, absent. †Covariates are conditioned on age, 55 years; sex, male; comorbidities, absent.

Table 3: **Mediation analyses**

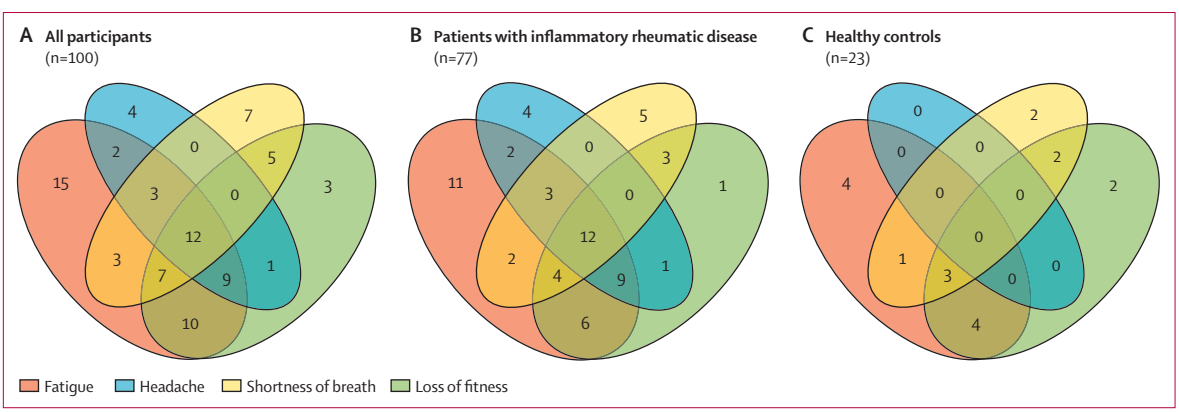


Figure 1: **Venn diagram of post-COVID condition symptoms**
Diagram depicts the relationship between the four most reported symptoms of post-COVID condition in all participants (A), patients with inflammatory rheumatic disease (B), and healthy controls (C).

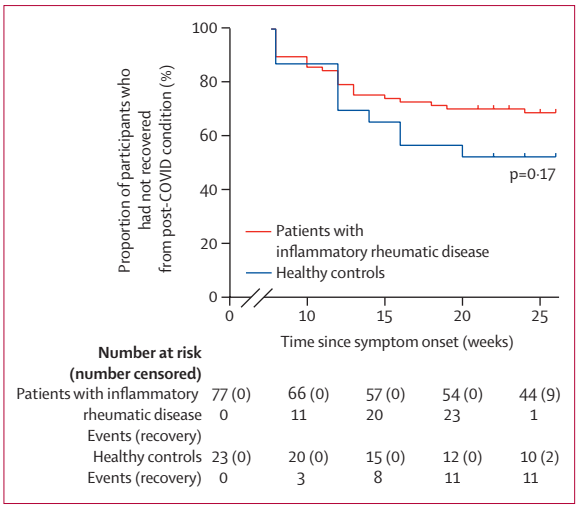
healthy controls, had a diagnosis of post-COVID condition established by a health-care professional.

Disease characteristics for participants who reported persistent symptoms (duration ≥8 weeks) during the first 2 years of the COVID-19 pandemic, stratified for participant status and history of COVID-19, are presented in the appendix (p 4). Persistent symptoms were reported more frequently by participants with a history of COVID-19 than by those without a history of COVID-19, and by patients with inflammatory rheumatic disease compared with healthy controls; 152 (43%) of 351 patients with inflammatory rheumatic disease versus 48 (33%) of 147 healthy controls with a history of COVID-19, and 346 (21%) of 1623 patients with inflammatory rheumatic disease versus 63 (11%) of 586 healthy controls without a history of COVID-19 (figure 3; appendix p 4). Notably, patients with inflammatory rheumatic disease who had a history of COVID-19 less frequently attributed persistent symptoms to post-COVID condition than did healthy controls; 50 (33%) of 152 patients with inflammatory rheumatic disease versus 30 (63%) of 48 healthy controls. The distribution of reported symptom types was similar across groups, but insomnia was more frequent in participants without a history of COVID-19 (appendix p 8).

Exploratory analyses to investigate whether unmeasured confounding could explain the observed association between participant status and post-COVID condition showed that the E-value was 1·96 (lower bound confidence interval E-value 1·16) for the crude model and 1·78 (lower bound confidence interval E-value 1·00) for the model adjusted for all potential measured confounders (table 2). Logistic regression analyses confirmed that patients with inflammatory rheumatic disease were more likely to report persistent symptoms that could also be observed in post-COVID condition during the first 2 years of the COVID-19 pandemic, and estimated ORs were similar to the calculated E-values (OR range, 1·62–2·52; table 2).

Discussion

In this study, we prospectively monitored patients with inflammatory rheumatic disease and healthy controls after a SARS-CoV-2 infection during the omicron-



Number at risk (number censored)					
Patients with inflammatory rheumatic disease	77 (0)	66 (0)	57 (0)	54 (0)	44 (9)
	0	11	20	23	1
Events (recovery)					
Healthy controls	23 (0)	20 (0)	15 (0)	12 (0)	10 (2)
Events (recovery)	0	3	8	11	11

Figure 2: **Kaplan-Meier curve of time until recovery from a post-COVID condition**
Only participants who met WHO criteria for post-COVID condition were included for analyses.

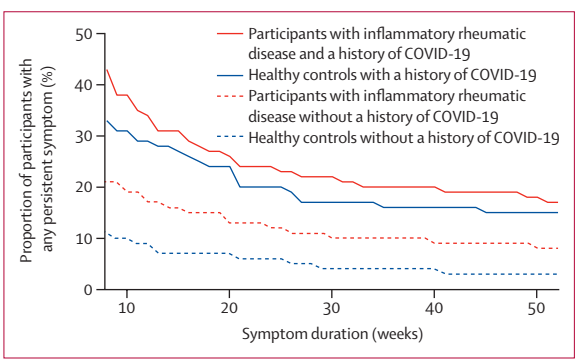


Figure 3: **Prevalence of persistent symptoms during the first 2 years of the COVID-19 pandemic**
Graph showing the proportion of participants with persistent symptoms for increasing total symptom duration, stratified by history of COVID-19 before Jan 1, 2022, and participant status.

dominant period. We observed that 21% of patients with inflammatory rheumatic disease and 13% of healthy controls had post-COVID condition according to WHO criteria. Type of symptoms and recovery time from post-COVID condition were similar for patients and controls. Notably, participants with inflammatory rheumatic disease without a history of COVID-19 were more likely to report persistent symptoms that are used to identify post-COVID condition during the first 2 years of the pandemic than were healthy controls. Finally, patients with inflammatory rheumatic disease more frequently sought contact with a health-care professional because of persistent symptoms after a SARS-CoV-2 infection than did healthy controls, primarily general practitioners, physiotherapists, and rheumatologists.

To our knowledge, this is the first large prospective study comparing the long-term consequences of COVID-19 between patients with inflammatory rheumatic disease and healthy controls. The observed proportion of patients with post-COVID condition after a SARS-CoV-2 infection with the omicron variant was considerably lower than reported in previous studies on post-COVID condition in patients with inflammatory rheumatic disease. For example, two retrospective cohort studies reported persistence of symptoms after a SARS-CoV-2 infection in 57% and 69% of patients with rheumatic diseases,[14,15] and two other cohort studies showed that 45% and 56% had prolonged symptom duration.[16,17] On the basis of these high proportions, it has been concluded that the risk of long-term health problems and the need for health care after a SARS-CoV-2 infection is high for patients with rheumatic diseases".[14–17] However, we should be careful when interpreting results from these studies. First, the studies of Leon and colleagues,[14] Brito-Zeron and colleagues,[15] and Di Iorio and colleagues[16] included participants after confirmation of a SARS-CoV-2 infection. This could introduce selection bias, as more severe COVID-19 cases are more likely to be PCR-confirmed than are mild or asymptomatic cases, and patients with more severe disease might be more willing to participate in COVID-19 research.[18] The proportion of participants admitted to hospital with COVID-19 in these studies is substantially higher than in our own previous observations; 45–69% versus 21%,[14,15] and the study population of Leon and colleagues exclusively consisted of participants in hospital with COVID-19.[14] Multiple studies have shown that a higher disease severity during the acute infection phase of SARS-CoV-2 is associated with an increased risk of prolonged symptom duration,[19–21] so it is likely that this overrepresentation of severe COVID-19 cases contributed to raising risk estimates for developing post-COVID condition. Second, Brito-Ziron and colleagues' and Barbhaiya and colleagues' studies were retrospective, and data were retrieved from medical health records or data registries.[15,17] The retrospective design increases the risk of selection bias and data accuracy is limited. Third, Brito-Zeron and colleagues' study found that 57% of patients with primary Sjögren's syndrome remained symptomatic after a median follow-up of 5 months after SARS-CoV-2 infection.[15] However, follow-up time ranged from 5 to 388 days, which means that even patients with a very short follow-up time after SARS-CoV-2 infection could contribute to increasing the final risk estimate. Fourth, all four of the aforementioned studies were done before the emergence of the omicron variant of SARS-CoV-2, which might reduce the generalisability to current SARS-CoV-2 infections due to the considerably lower virulence of the omicron variant than previous variants.[14–17] In the present study, participants were included before infection with SARS-CoV-2 and longitudinally evaluated after PCR-confirmed or antigen-confirmed SARS-CoV-2 infections during the omicron-dominant period. This study design minimises selection bias and optimises data validity and reliability, making it

more likely that the results more accurately reflect the true risk of developing post-COVID condition in patients with inflammatory rheumatic disease compared with results of the aforementioned studies, at least for infections with the omicron variant.

In the current study, we simultaneously investigated patients with inflammatory rheumatic disease and healthy controls, which allowed us to directly assess whether patients with inflammatory rheumatic disease are more susceptible to post-COVID condition than are people from the general population. The inclusion of a control group is highly relevant for research into post-COVID condition, since the large amount of heterogeneity between studies considerably limits between-study comparisons.[22] This between-study heterogeneity is mainly caused by the broad and non-specific definition of post-COVID condition, which includes any persistent subjective symptom after a SARS-CoV-2 infection as long as alternative causes cannot be identified.[3] Consequently, more than 50 symptoms have already been identified,[23] but most studies have reported fatigue, dyspnea, neurocognitive symptoms (eg, brain fog), and musculoskeletal symptoms (eg, myalgia or arthralgia) in people from the general population.[24] This symptomology corresponds with results from post-COVID condition studies in patients with rheumatic diseases,[14–17] and is in line with our own observations that both symptomology and recovery time from post-COVID condition were similar between patients with inflammatory rheumatic disease and healthy controls. However, we also observed that the prevalence of post-COVID condition after SARS-CoV-2 omicron infections was 1·7 times higher in patients with inflammatory rheumatic disease than in controls, which contradicts the results of a retrospective study done in participants with COVID-19 in hospital.[25] However, the current clinical picture of post-COVID condition bears considerable overlap with disease manifestations of rheumatic diseases,[5,23] which might lead to overestimated risk estimates due to the increased possibility of falsely attributing clinical manifestations of rheumatic diseases to post-COVID condition. In exploratory analyses that investigated unmeasured confounding, we demonstrated that patients with inflammatory rheumatic disease who had not had COVID-19 were more likely to report persistent symptoms that are used to identify post-COVID condition than were healthy controls, and that this association reached the necessary strength to account for the higher proportion of post-COVID condition in patients with inflammatory rheumatic disease than healthy controls. Additionally, patients with inflammatory rheumatic disease reported more severe symptoms during the acute infection phase of SARS-CoV-2 than did controls, but disease severity mediated less than 20% of the association between participant status and post-COVID condition. Collectively, our data highlight the limitations of applying current criteria of post-COVID condition in patients with inflammatory rheumatic disease. We therefore believe that data from studies on post-COVID condition in patients with inflammatory rheumatic disease should be interpreted with caution, and that it might be appropriate for rheumatologists to have a nuanced attitude when communicating the long-term risks of COVID-19 to their patients.

Important strengths of our study include the prospective follow-up of a large cohort of patients with various inflammatory rheumatic diseases and the inclusion of a large group of simultaneously enrolled age-matched and sex-matched healthy controls. Additionally, the response rate of COVID-19 sequalae questionnaires used for prospective monitoring after SARS-CoV-2 omicron infections was almost 80%, which is considered to be high.[26] Furthermore, participants were included before infection with SARS-CoV-2, which minimises the risk of overrepresentation of severe COVID-19 cases and thus selection bias. Furthermore, we addressed and quantified systematic differences in the reporting of symptoms used to define post-COVID condition between patients with inflammatory rheumatic disease and people from the general population, which had already been hypothesised to be a potentially relevant source of unmeasured confounding by others.[5,23] Finally, we investigated the health-care utilisation of patients with inflammatory rheumatic disease and healthy controls with persistent symptoms after SARS-CoV-2 infections, as it is important to know which health-care professionals are likely to encounter these patients. We observed that patients with inflammatory rheumatic disease more frequently contacted health-care professionals for persistent symptoms than did healthy controls, primarily a general practitioner, physiotherapist, or rheumatologist. However, the threshold for visiting health-care professionals because of persistent symptoms might be lower for patients with inflammatory rheumatic disease than healthy controls, because they require multiple and frequent interactions with physicians because of their underlying condition. This could, in part, explain the difference between patients and controls in the number of times they contacted health-care professionals for persistent symptoms. Our data also imply that health care for patients with inflammatory rheumatic disease in the Netherlands who experience persistent symptoms after SARS-CoV-2 infections does not remain exclusively within the domain of rheumatologists, so knowledge distribution regarding epidemiology and disease presentation and prognosis of post-COVID condition in patients with inflammatory rheumatic disease beyond the borders of rheumatology has important value.

Our study also has several limitations. First, data on the occurrence of persistent symptoms during the first 2 years of the COVID-19 pandemic were collected retrospectively, which negatively affects data accuracy. It

might also introduce recall bias, as participants with a history of COVID-19 might recall persistent symptoms more accurately than those without a history of COVID-19. Although this does not result in systematic differences between patients and controls, this part of our data should be interpreted with caution. Second, follow-up questionnaires after SARS-CoV-2 infections were sent to participants at fixed timepoints independent of the timing of a SARS-CoV-2 infection, which means that the time between SARS-CoV-2 infection and survey completion differs between individuals. However, the mean time between infection onset and survey completion was similar for patients with inflammatory rheumatic disease and healthy controls, so we do not expect that this negatively affects the validity of our comparisons between the two groups. Third, despite the large number of participants included in our cohort, the number of participants, especially healthy controls, who developed post-COVID condition after an omicron infection were few. This, combined with the diagnostic uncertainty of post-COVID condition that entails a considerable risk of misclassification, limits our ability to draw definitive conclusions regarding the risk of post-COVID condition for patients with inflammatory rheumatic disease compared with people from the general population. Fourth, post-COVID condition cases were identified via a questionnaire and not via individual assessment by health-care physicians. Other potential causes of persistent symptoms could therefore not be ruled out in participants who did not visit a physician, so our findings might be somewhat overestimated. This overestimation is probably more pronounced in patients with inflammatory rheumatic disease than in healthy controls due to similarities in the disease presentation of post-COVID condition and the underlying rheumatic disease. Finally, we collected data up to 26 weeks of follow-up after the onset of infection, but a considerable proportion of patients with inflammatory rheumatic disease and healthy controls with post-COVID condition still had unresolved symptoms at that time. Longer follow-up will therefore be necessary to draw definitive conclusions about recovery time from post-COVID condition.

In summary, we found that 21% of patients with inflammatory rheumatic disease and 13% of healthy controls developed post-COVID condition after a SARS-CoV-2 omicron infection based on WHO-criteria. Furthermore, symptomology and recovery time from post-COVID condition were similar between patients and controls. We also found that more patients with inflammatory rheumatic disease than healthy controls without a history of COVID-19 reported symptoms that are also observed in post-COVID condition, and this association reached the strength that is necessary to negate the difference in post-COVID condition between patients and controls. Therefore, it is possible that the observed difference in post-COVID condition between patients and controls could be partly explained by clinical manifestations in the context of underlying rheumatic diseases. Our study highlights the limitations of applying current criteria for post-COVID condition in patients with inflammatory rheumatic disease, and suggests it might be appropriate for physicians to have a nuanced attitude when communicating the long-term consequences of COVID-19 to their patients.

Contributors

LB wrote the first draft of the manuscript and all other authors revised the manuscript for important intellectual content. LB and FH directly accessed and verified the underlying data and performed the statistical analyses. TR and MS did the serological assays and all other authors contributed to data acquisition. All authors met the criteria for authorship set by the International Committee of Medical Journal Editors. All authors confirm that they had full access to all data in the study, and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Aggregated data and code for reproducing the results of this analysis can be shared upon reasonable request to the corresponding author.

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