CLINICAL SCIENCE

Impact of vaccination on postacute sequelae of SARS CoV-2 infection in patients with rheumatic diseases

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ABSTRACT

Objective Vaccination decreases the risk of severe COVID-19 but its impact on postacute sequelae of COVID-19 (PASC) is unclear among patients with systemic autoimmune rheumatic diseases (SARDs) who may have blunted vaccine immunogenicity and be vulnerable to PASC.

Methods We prospectively enrolled patients with SARD from a large healthcare system who survived acute infection to complete surveys. The symptom-free duration and the odds of PASC (any symptom lasting ≥28 or 90 days) were evaluated using restricted mean survival time and multivariable logistic regression, respectively, among those with and without breakthrough infection (≥14 days after initial vaccine series).

Results Among 280 patients (11% unvaccinated; 48% partially vaccinated; 41% fully vaccinated), the mean age was 53 years, 80% were female and 82% were white. The most common SARDs were inflammatory arthritis (59%) and connective tissue disease (24%). Those with breakthrough infection had more upper respiratory symptoms, and those with non-breakthrough infection had more anosmia, dysgeusia and joint pain. Compared with those with non-breakthrough COVID-19 infection (n=164), those with breakthrough infection (n=116) had significantly more symptom-free days over the follow-up period (+21.4 days, 95% CI 0.95 to 41.91; p=0.04) and lower odds of PASC at 28 and 90 days (adjusted OR, aOR 0.49, 95% CI 0.29 to 0.83 and aOR 0.10, 95% CI 0.04 to 0.22, respectively).

Conclusion Vaccinated patients with SARDs were less likely to experience PASC compared with those not fully vaccinated. While we cannot rule out the possibility that findings may be due to intrinsic differences in PASC risk from different SARS-CoV-2 variants, these findings support the benefits of vaccination for patients with SARDs and suggest that the immune response to acute infection is important in the pathogenesis of PASC in patients with SARDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Postacute sequelae of COVID-19 (PASC) affects many COVID-19 survivors, though the impact of vaccination on the risk and severity of PASC is unclear, especially among those with systemic autoimmune rheumatic diseases (SARDs) who may have impaired responses to vaccines and be particularly vulnerable to PASC.

WHAT THIS STUDY ADDS

⇒ In this prospective cohort of patients with SARD, we found that those with vs without breakthrough infection had more symptom-free days over the follow-up period (+21.4 days, 95% CI 0.95 to 41.91; p=0.04) and a lower odds of PASC at 28 days (adjusted OR, aOR 0.49, 95% CI 0.29 to 0.83) and at 90 days (aOR 0.10, 95% CI 0.04 to 0.22).

⇒ Patient-reported pain and fatigue scores were lower, reflecting less severe pain and fatigue, in those with breakthrough infection compared with those with non-breakthrough infection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies are needed to determine how additional vaccine doses, early outpatient treatment and immunomodulating medications may affect PASC risk among patients with SARDs.

INTRODUCTION

Patients with systemic autoimmune rheumatic diseases (SARDs) are at higher risk of severe acute outcomes of COVID-19 infection, though few studies have investigated the risk of longer-term complications of COVID-19.[1–7] Vaccines are safe and efficacious in reducing risk for severe COVID-19 among patients with SARD, but less is known about how they may impact the risk of postacute sequelae of COVID-19 (PASC).

PASC most often refers to either persistent or new-onset symptoms following acute infection and is typically defined by duration of symptoms, with some definitions requiring symptoms that persist for at least 1 month and others for at least 3 months following acute infection.[8 9] PASC incorporates a heterogeneous set of symptoms that may include impaired executive function, fatigue, dyspnoea, cough, palpitations, myalgias or arthralgias, and/or anosmia, among others. A higher severity of acute COVID-19 is associated with a greater risk of PASC, though asymptomatic patients or those with minimal symptoms can also develop PASC.[1 10 11] Estimates of PASC vary, with population-based studies, suggesting that PASC

affects anywhere from less than 10% to between 20% and 40% of people after acute infection; up to 50%–70% of patients because of COVID-19 may continue to have symptoms months following hospital discharge.[10–15] Patients with SARDs may be vulnerable to PASC due to altered immunity, immunosuppressive therapy, and increased risk for severe acute COVID-19.

While vaccination against SARS-CoV-2 decreases the risk of severe acute outcomes, there are limited data regarding the effect of vaccination on PASC risk.[16 17] Previous studies of patients without SARDs have suggested a decreased risk of PASC in those who were vaccinated prior to COVID-19 infection.[18–20] However, many patients with SARDs have impaired responses to the SARS-CoV-2 vaccine and may not similarly benefit from vaccination with regard to the risk of PASC.[21–25] In this study, we investigated the association of SARS-CoV-2 vaccination with the risk of PASC in patients with SARDs.

METHODS

Study population and patient identification

We performed a prospective study in Mass General Brigham (MGB), a large, multicentre healthcare system that includes 2 tertiary care hospitals (Massachusetts General Hospital and Brigham and Women's Hospital), 12 community hospitals and their associated primary and specialty outpatient centres in the greater Boston, Massachusetts, area. We identified patients within MGB who were ≥18 years of age, had a positive test result for SARS-CoV-2 by PCR or antigen nasopharyngeal test between 1 March 2020 and 8 July 2022, and had an immune-mediated disease diagnosis based on billing codes. Our study population was limited to patients with confirmed SARDs. Diagnosis of a prevalent SARD at the time of infection was confirmed by manual review of the electronic health record (EHR) in our final study population. This approach has been previously described.[2 6 7]

Patient recruitment for prospective study

From this population, we invited patients who survived their acute infection to participate in a prospective, longitudinal study: COVID-19 and Rheumatic Diseases (RheumCARD). As previously described in detail, potential participants were invited to participate either via secure online EHR portal or US mail.[2] Initial invitations were sent on 11 March 2021, and as new subjects with confirmed infection were identified, subsequent patients were invited on a rolling basis, approximately once per month, at least 28 days following their COVID-19 diagnosis date.

Data Collection

Demographic data assessed in the survey included age, sex, race and ethnicity. Smoking status was assessed as never, past or current. The comorbidity count was derived as the sum of comorbidities queried. COVID-19 symptoms assessed in the survey included fever, sore throat, new cough, nasal congestion/rhinorrhoea, dyspnoea, chest pain, rash, myalgia, fatigue/malaise, headache, nausea/vomiting, diarrhoea, anosmia, dysgeusia and joint pain. The symptom count was calculated as the sum of these self-reported symptoms. We collected details of the acute COVID-19 course, including symptom duration, treatments and details of hospitalisation (if applicable). Time to COVID-19 symptom resolution and vaccination status were collected.

SARDs were categorised broadly as inflammatory arthritis (including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthropathy or other inflammatory arthritis), vasculitis (including ANCA-associated vasculitis, giant cell arteritis and/or polymyalgia rheumatica, or other vasculitis such as Takayasu arteritis or Kawasaki disease), connective tissue disease (CTD, including systemic lupus erythematosus, mixed connective tissue disease, undifferentiated connective tissue disease, idiopathic inflammatory myopathy or Sjogren's syndrome) or other (sarcoidosis, Behcet disease, IgG_4-related disease or relapsing polychondritis). Use of immunomodulator medications at the time of acute COVID-19 infection was assessed.

Exposure of interest

The exposure of interest was being fully vaccinated at COVID-19 onset vs partially vaccinated or unvaccinated. Based on patient report, we classified patients as fully vaccinated at the index date (date of COVID-19 diagnosis) if infection was ≥14 days after completion of their primary vaccine series according to the US Centers for Disease Control and Prevention (CDC) definition: two doses of a messenger RNA (mRNA) SARS-CoV-2 vaccine (ie, either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)) or one dose of the Ad26.COV2.S (Johnson & Johnson-Janssen) vaccine.[26] Other patients were classified as either partially vaccinated or unvaccinated at the index date.

Outcome assessments

The primary outcome was PASC, defined as any persistent symptom at least 28 days post-COVID-19 infection (US CDC definition).[9] A secondary outcome was PASC, as defined by any persistent symptom at least 90 days post-COVID-19 infection (WHO definition).[8] All patients were enrolled at least 28 days after their COVID-19 diagnosis. Only those who completed the surveys at least 90 days following their COVID-19 diagnosis were included in the analysis of the WHO definition of PASC. Symptom duration (in days) and symptom-free days were other secondary outcomes; days of symptoms were counted from the index date through the time of symptom resolution or date of survey completion if symptoms were ongoing. Patients with missing data regarding symptom duration or vaccination status were excluded.

Other secondary outcomes included pain (measured by the short-form McGill Pain Questionnaire (SF-MPQ[27]), fatigue (Fatigue Symptom Inventory (FSI[28 29]) and functional status (modified Health Assessment Questionnaire (mHAQ[30]). The 12-item SF health survey (SF-12) was used as a general measure of both physical and mental health status.[31] A Physical Component Summary Score (PCS-12) and Mental Component Summary Score (MCS-12) were calculated. Among those who developed PASC, we compared pain, fatigue, functional status and overall health status scores between those with PASC following breakthrough versus non-breakthrough COVID-19 infection. We also assessed rheumatic disease activity following COVID-19 infection, based on self-reported SARD flare, participant global assessment, and disease activity, as assessed by the RAPID-3 score.

Outcomes were assessed from 11 March 2021 (the time of completion of the first survey) to 8 August 2022 (the time of completion of the last survey at the time of manuscript preparation).

Statistical analysis

Categorical variables are presented as number (percentage), and continuous variables are presented as mean±SD or median±IQR, as appropriate. Continuous variables were compared

using a two-sample t-test for continuous normally distributed variables or Wilcoxon test for continuous non-normally distributed variables. Categorical variables were compared by using χ^2 tests.

To assess differences in the symptom-free time between those with breakthrough versus non-breakthrough infection, we used restricted mean survival time (RMST).[32–34] The event in this analysis was the number of days to COVID-19 symptom resolution. We compared the areas under the cumulative incidence curves, representing the number of days following symptom resolution (symptom-free days). Thus, the difference between the two groups reflects the difference in the number of symptom-free days between the two groups, with the non-breakthrough group as the reference group. RMST has multiple strengths, including no required assumptions regarding proportional hazards as well as ease of interpretation (effect estimate in difference in number of days as opposed to an HR). Our primary follow-up period was 204 days, given that this was the maximum follow-up period among those with breakthrough infections. We performed secondary analyses assessing these outcomes at 28 and 90 days.

We calculated ORs for PASC at 28 and 90 days using unadjusted and multivariable adjusted logistic regression. The first multivariable model adjusted for age, sex and race. The second multivariable model adjusted for age, sex, race, comorbidity count and use of any one of the following medications: anti-CD20 monoclonal antibodies, methotrexate, mycophenolate or glucocorticoids. These medications were chosen because of their impact on SARS-CoV-2 vaccine immunogenicity.

To assess the robustness of our findings, we conducted four sensitivity analyses evaluating ORs for PASC as well as differences in other patient-reported outcomes, limiting the population to: (1) those who did not receive nirmatrelvir/ritonavir or monoclonal antibodies, (2) those who did not receive any COVID-19-related treatment, (3) those who completed the questionnaires within 6 months of COVID-19 infection and (4) those who did not require hospitalisation for acute COVID-19 infection.

The level of significance was set as a two-tailed $p<0.05$, and statistical analyses were completed using SAS statistical software (V.9.4; SAS Institute).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Participant characteristics

Of 1308 patients invited, 305 completed surveys (23% response rate), and of these, we analysed 280 patients with SARDs who survived COVID-19. One hundred and sixteen (41%) had a breakthrough COVID-19 infection and the remainder (164, 59%) were either unvaccinated or were partially vaccinated at the time of diagnosis and were considered to have non-breakthrough COVID-19 infection. The breakthrough and non-breakthrough groups were similar with respect to age, sex, race, ethnicity, smoking status and SARD category (table 1).

The majority in each group were female (80% of those with breakthrough infection vs 79% of those with non-breakthrough infection, p=0.88), and the mean age at the time of survey completion was 53 vs 52 years, respectively (p=0.68). Most patients in each group (breakthrough vs non-breakthrough, respectively) were white (87% vs 79%, p=0.08) and never smokers (75% vs 71%, p=0.65). Common comorbidities in each group (breakthrough vs non-breakthrough, respectively) were also similar with the exception of obesity which was more common in those with non-breakthrough infection (25% vs 15%, p=0.04). The median (IQR) comorbidity count was 1 (0, 1) in those with breakthrough infection compared with 1 (0, 2) in those with non-breakthrough infection (p=0.68).

The most common SARD category (in those with breakthrough vs non-breakthrough infection, respectively) was inflammatory arthritis (53% vs 63%), followed by connective tissue disease (26% vs 23%), vasculitis (11% vs 8%), other disease (6% vs 3%), or multiple diseases (4% vs 2%) (p=0.33 for difference across categories). The most common conventional synthetic DMARDs used at the time of COVID-19 included hydroxychloroquine (29% vs 18%, p=0.04), methotrexate (23% vs 20%, p=0.567) and mycophenolate (12% vs 4%, p=0.02). The most common biologic and targeted synthetic DMARDs at the time of COVID-19 infection included TNF inhibitors (24% vs 21%, p=0.66) followed by anti-CD20 monoclonal antibodies (12% vs 5%, p=0.08) and Janus kinase inhibitors (6% vs 4%, p=0.40).

Postacute sequelae according to breakthrough infection status

Over 204 days, the mean time spent free from symptoms (time postsymptom resolution), reflected by the area under the cumulative incidence curves, was 133.8 days in the breakthrough group and 112.4 days in the non-breakthrough group (table 2; figure 1; Online supplemental file 2). Thus, the breakthrough group was symptom-free for an additional 21.4 days (95% CI 0.95 to 41.91, p=0.04) compared with the non-breakthrough group. The breakthrough group also experienced more symptom-free days over follow-up time when limited to 28 and 90 days (online supplemental figures 2 and 3). Those with breakthrough infection were less likely to have PASC at 28 days (41% vs 54%, p=0.04) and at 90 days (21% vs 41%, p<0.0001) (table 2; figure 2), corresponding to a lower odds of PASC at 28 days (adjusted OR, aOR 0.49, 95% CI 0.29 to 0.83) and 90 days (aOR 0.10, 95% CI 0.04 to 0.22).

Our findings remained consistent in sensitivity analyses limiting the sample to those who did not receive nirmatrelvir/ritonavir or monoclonal antibodies, those who did not receive any COVID-19-related treatment, those who completed the questionnaires within 6 months of COVID-19 infection and those who did not require hospitalisation (online supplemental tables 1–4).

Acute COVID-19 symptoms and clinical course according to breakthrough infection status

Infection during the period in which the Omicron variants were predominant (17 December 2021 onward) was more common in patients with breakthrough COVID-19 infection (84, 72%) than in patients with non-breakthrough COVID-19 infection (3, 2%) (table 3). Those with breakthrough infection had more nasal congestion/rhinorrhoea (73% vs 46%, p<0.0001) and sore throat (54% vs 37%, p=0.01), and those with non-breakthrough infection had more anosmia (46% vs 22%, p<0.0001), dysgeusia (45% vs 28%, p<0.01) and joint pain (11% vs 4%, p=0.05). Those with breakthrough infection more often received nirmatrelvir/ritonavir (12% vs 1%, p<0.0001) and monoclonal antibody treatment (34% vs 8%, p<0.0001) compared with those with non-breakthrough infection. Fewer patients with breakthrough COVID-19 infection required hospitalisation than those with non-breakthrough infection (5% vs 27%, p=0.001).

Table 1 Demographics and rheumatic disease characteristics of patients with history of COVID-19 infection

Characteristic	All rheumatic disease patients (N=280)	Breakthrough COVID-19 infection (N=116)	Non-breakthrough COVID-19 infection (N=164)	P value
Age at time of COVID-19 symptom onset in years, mean±SD	52 (15)	53 (15)	51 (16)	0.48
Age at time of survey in years, mean±SD	53 (15)	53 (15)	52 (16)	0.68
Female, n (%)	223 (80)	93 (80)	130 (79)	0.88
Race, n (%)				
Asian	12 (4)	5 (4)	7 (4)	1.00
Black	20 (7)	4 (3)	16 (10)	0.06
White	230 (82)	101 (87)	129 (79)	0.08
Other	15 (5)	6 (5)	9 (5)	1.00
Unknown	7 (3)	3 (3)	4 (2)	1.00
Hispanic or Latinx ethnicity	27 (10)	8 (7)	19 (12)	0.15
Smoking status				0.65
Current	4 (1)	2 (2)	2 (1)	
Former	72 (26)	27 (23)	45 (27)	
Never	203 (73)	87 (75)	116 (71)	
SARD category*				0.33
Inflammatory arthritis	165 (59)	61 (53)	104 (63)	
Connective tissue disease	68 (24)	30 (26)	38 (23)	
Vasculitis	26 (9)	13 (11)	13 (8)	
Multiple	9 (3)	5 (4)	4 (2)	
Other	12 (4)	7 (6)	5 (3)	
Immunomodulatory medications				
cs DMARDs				
Antimalarial (includes hydroxychloroquine and chloroquine)	64 (23)	34 (29)	30 (18)	0.04
Methotrexate	60 (21)	27 (23)	33 (20)	0.56
Mycophenolate mofetil/mycophenolic acid	21 (8)	14 (12)	7 (4)	0.02
Other csDMARD†	25 (9)	14 (12)	11 (7)	0.14
Targeted synthetic DMARD (JAK inhibitor)	13 (5)	7 (6)	6 (4)	0.40
Biologic DMARDs				
Anti-CD20 monoclonal antibody	23 (8)	14 (12)	9 (5)	0.08
TNF inhibitor	63 (22)	28 (24)	35 (21)	0.66
Other biologic DMARD‡	35 (13)	15 (13)	20 (12)	0.86
Baseline glucocorticoid use at COVID-19 onset	51 (18)	24 (21)	27 (16)	0.43
Dose (prednisone-equivalent, daily mg), median (IQR)	9 (5–15)	8 (5–20)	10 (5–15)	0.43
Comorbidities				
Obesity	58 (21)	17 (15)	41 (25)	0.04
Hypertension	64 (23)	28 (24)	36 (22)	0.67
Asthma	49 (18)	23 (20)	26 (16)	0.43
Obstructive sleep apnoea	21 (8)	7 (6)	14 (9)	0.50
Coronary artery disease	18 (6)	6 (5)	12 (7)	0.62
Diabetes	16 (6)	7 (6)	9 (5)	1.00
Heart failure	6 (2)	2 (2)	4 (2)	1.00
Chronic kidney disease	12 (4)	7 (6)	5 (3)	0.24
Chronic obstructive pulmonary disease	4 (1)	2 (2)	2 (1)	1.00
Interstitial lung disease/pulmonary fibrosis	9 (3)	5 (4)	4 (2)	0.50
Solid tumour	4 (1)	1 (1)	3 (2)	0.64
Comorbidity count, median (IQR)	1 (0–2)	1 (0–1)	1 (0–2)	0.68

*For patients who reported multiple SARD diagnoses, those who reported inflammatory arthritis in addition to either lupus or myositis were classified as having a 'connective tissue disease (CTD)' given that inflammatory arthritis can be a component of CTD. Patients who listed both polymyalgia rheumatica and rheumatoid arthritis were classified as having 'inflammatory arthritis'. Patients with multiple SARDs that can coexist (eg, psoriatic arthritis and lupus) were classified as having multiple SARDs. In the case of missing data or unanswered survey questions regarding rheumatic disease diagnosis or treatment, manual review of the EHR was performed to fill in this missing data.
†Other conventional synthetic DMARD includes leflunomide, azathioprine, sulfasalazine, apremilast, cyclosporine and tacrolimus
‡Other biological DMARD includes IL-6 receptor inhibitor, B-cell activating factor inhibitor, IL-23 inhibitor, IL-17 inhibitor, IL-12/IL-23 inhibitor, IL-1 inhibitor and CTLA-4 immunoglobulin
csDMARD, conventional synthetic disease-modifying antirheumatic drug; EHR, electronic health record; JAK, janus kinase; SARD, systemic autoimmune rheumatic disease.

Table 2 Duration of symptoms and postacute sequelae of COVID-19 (PASC) following breakthrough versus non-breakthrough COVID-19 infection

	Breakthrough COVID-19 infection (N=116)	Non-breakthrough COVID-19 infection (N=164)	P value
Symptom-free days during 204-day* follow-up, mean	133.8	112.4	0.04
Difference in symptom-free days (95% CI)	21.40 (0.95 to 41.91)	Reference	0.04
CDC definition of PASC (COVID-19 symptoms lasting at least 28 days post-COVID-19 infection), n (%)	48 (41)	89 (54)	0.04
Unadjusted OR (95% CI)	0.59 (0.37 to 0.96)	Reference (1.0)	0.03
Adjusted OR (95% CI), Model 1†	0.52 (0.31 to 0.86)	Reference (1.0)	0.01
Adjusted OR (95% CI), Model 2†	0.49 (0.29 to 0.83)		0.01
WHO definition of PASC (COVID-19 symptoms lasting at least 90 days post-COVID-19 infection), n (%)‡	10 (21)	65 (41)	0.01
Unadjusted OR (95% CI)	0.14 (0.07 to 0.30)	Reference (1.0)	<0.0001
Adjusted OR (95% CI), Model 1†	0.11 (0.05 to 0.24)	Reference (1.0)	<0.0001
Adjusted OR (95% CI), Model 2†	0.10 (0.04 to 0.22)	Reference (1.0)	<0.0001

*Primary follow-up period was 204 days, given that this was the maximum follow-up period among those with breakthrough infections
†Multivariable model one is adjusted for age, sex and race. Multivariable model two is adjusted for age, sex, race, comorbidity count and use of any one of the following medications: anti-CD20 monoclonal antibodies, methotrexate, mycophenolate or glucocorticoids.
‡Denominator includes those who completed a survey at least 90 days following COVID-19 diagnosis; N=47 with breakthrough infection and 159 with non-breakthrough infection
CDC, Centres for Disease Control and Prevention; WHO, World Health Organization.

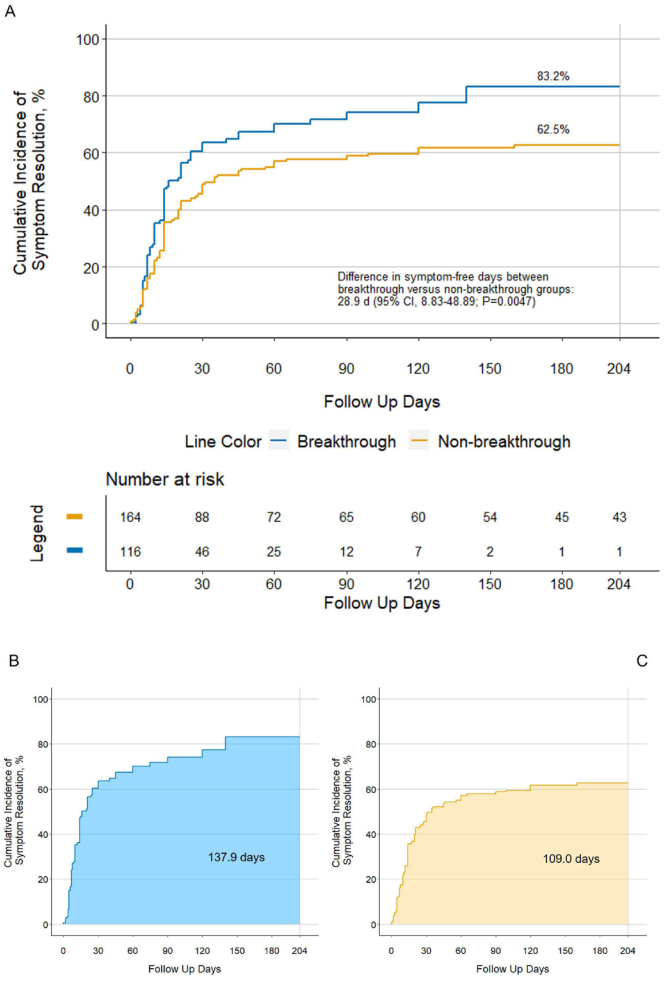

Figure 1 Adjusted days to symptom resolution in those with breakthrough versus non-breakthrough COVID-19 infection over 204-day follow-up period. PASC, postacute sequelae of COVID-19. (A) Cumulative incidence curves for time to symptom resolution, comparing breakthrough versus non-breakthrough infection. (B and C), mean post-symptom resolution time spans as the area under the cumulative incidence curves in those with breakthrough versus nonbreakthrough infection, respectively, across 204 days of follow-up.

Patient-reported outcomes including pain, fatigue, functional status and rheumatic disease activity following COVID-19 infection

Pain and fatigue were less severe in those with breakthrough infection than in those with non-breakthrough infection (SF-MPQ: median score of 4 vs 5, p=0.04 and FSI: 48 vs 55, p=0.08, respectively) (figure 3A,B; table 4). Functional status (mHAQ) scores were similar between those with and without breakthrough COVID-19 infection (median of 0.1 in each group, p=0.88) (figure 3C). Health-related quality of life, as assessed by the SF-12, was similar among those with and without breakthrough infection (figure 3D). The median (IQR) PCS-12 was 43.6 (33.7, 52.6) in those with breakthrough infection compared with 41.0 (32.2, 49.5) in those with non-breakthrough infection (p=0.11), and the median (IQR) MCS-12 was 49.4 (41.4, 55.6) in those with breakthrough infection compared with 50.2 (37.9, 57.0) in those with non-breakthrough infection (p=0.86).

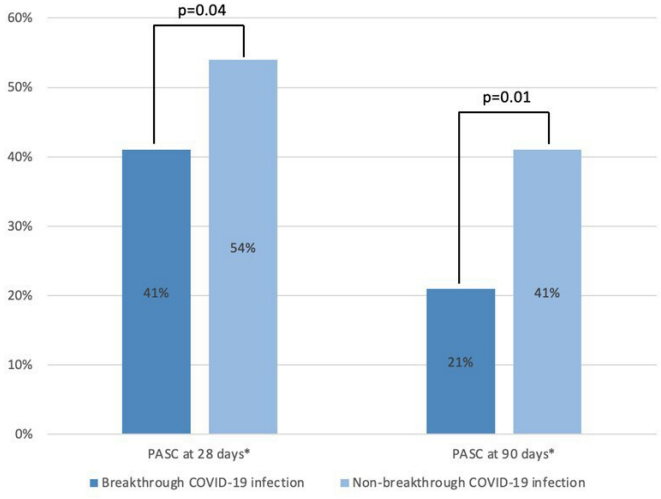

Figure 2 Proportion experiencing postacute sequelae of SARS CoV-2 among those with breakthrough and non-breakthrough COVID-19 infection. *Based on the Centers for Disease Control and Prevention Definition of PASC (COVID19 symptoms lasting at least 28 days post-COVID-19 infection) or the World Health Organization Definition of PASC (COVID-19 symptoms lasting at least 90 days post-COVID-19 infection)

Table 3 Symptoms and clinical course for study participants with rheumatic disease and COVID-19, stratified by vaccination status at the time of infection

	All rheumatic disease patients (N=280)	Breakthrough COVID-19 infection (N=116)	Non-breakthrough COVID-19 infection (N=164)	P value
Date of COVID-19 diagnosis, n (%)				<0.0001
March 1–June 30, 2020	45 (16)	0 (0)	45 (27)	
July 1, 2020–January 31, 2021	97 (35)	0 (0)	97 (59)	
February 1–June 30, 2021	21 (8)	3 (3)	18 (11)	
July 1–December 16, 2021	30 (11)	29 (25)	1 (1)	
December 17, 2021–July 8, 2022	87 (31)	84 (72)	3 (2)	
COVID-19 symptoms, n (%)				
Fatigue/malaise	220 (79)	93 (80)	127 (77)	0.66
Fever	165 (59)	66 (57)	99 (60)	0.62
Headache	175 (63)	71 (61)	104 (63)	0.71
Myalgias	162 (58)	63 (54)	99 (60)	0.33
Nasal congestion or rhinorrhoea	160 (57)	85 (73)	75 (46)	<0.0001
Cough	146 (52)	73 (63)	73 (45)	<0.01
Anosmia	101 (36)	25 (22)	76 (46)	<0.0001
Dysgeusia	106 (38)	32 (28)	74 (45)	<0.01
Sore throat	124 (44)	63 (54)	61 (37)	<0.01
Dyspnoea	83 (30)	28 (24)	55 (34)	0.11
Chest pain	59 (21)	25 (22)	34 (21)	0.88
Nausea or vomiting	44 (16)	16 (14)	28 (17)	0.51
Joint pain	23 (8)	5 (4)	18 (11)	0.049
New rash, hives or blisters	17 (6)	4 (3)	13 (8)	0.14
None	64 (23)	39 (34)	25 (15)	<0.01
Acute COVID-19 treatment, n (%)				
Dexamethasone	17 (6)	3 (3)	14 (9)	0.04
Remdesivir	12 (4)	3 (3)	9 (5)	0.37
Monoclonal antibody	52 (19)	39 (34)	13 (8)	<0.0001
Nirmatrelvir/ritonavir	15 (5)	14 (12)	1 (1)	<0.0001
COVID-19 severity, n (%)				<0.01
Not hospitalised	244 (87)	110 (95)	134 (81)	
Hospitalised with or without supplemental oxygen	32 (11)	5 (4)	27 (16)	

Patient-reported outcome measures comparing PASC following breakthrough COVID-19 infection (n=48) vs PASC following non-breakthrough COVID-19 infection (n=89) were similar in terms of pain, fatigue, functional status and overall health status (online supplemental table 5). The frequency and timing relative to infection of self-reported flares of the underlying SARD were also similar following COVID-19 infection in those with breakthrough versus non-breakthrough infection (40% vs 42%, p=0.71) (online supplemental table 6).

DISCUSSION

In this prospective study of patients with SARDs and COVID-19, those with breakthrough infection had significantly shorter symptom duration and lower rates of PASC than those unvaccinated or partially vaccinated prior to infection. This corresponded with less pain and fatigue, two common manifestations of PASC, in those with breakthrough infection compared with those with non-breakthrough infection following the acute course. Collectively, our findings suggest that SARS-CoV-2 vaccination reduces the risk of PASC in patients with SARD, in addition to the known reduction in the risk of severe acute COVID-19 outcomes. These results provide further rationale for vaccination among patients with SARD.

There are limited data regarding the potential impact of SARS-CoV-2 vaccination on the risk of PASC in the general population and, to our knowledge, no studies in patients with SARDs. A previous community-based study of the general population in the United Kingdom found a nearly 50% reduced risk of PASC (≥ 28 days) in those with a breakthrough infection (OR 0.51, 95% CI 0.32 to 0.82).[18] Similar findings were observed in a cohort study of the Israeli general population after COVID-19.[35] Further, a large study conducted among Veterans Affairs beneficiaries found that the risk of cardiovascular, pulmonary, metabolic and coagulopathic sequelae was lower in those with breakthrough COVID-19.[19] Our findings expand on these prior studies, providing important new evidence in patients with SARD suggesting that despite concerns regarding the impact of SARD diagnoses and their treatments on vaccine immunogenicity, vaccination provides important long-term benefits after acute COVID-19.

Due to the timing of introduction of SARS-CoV-2 vaccines, calendar time varied between those with and without breakthrough infection. Those with breakthrough infection were more often infected later in the pandemic when the Delta and Omicron variants were predominant. It is therefore possible that our findings may be the result of differences in the SARS-CoV-2 variants rather than the effects of vaccination. Some prior studies

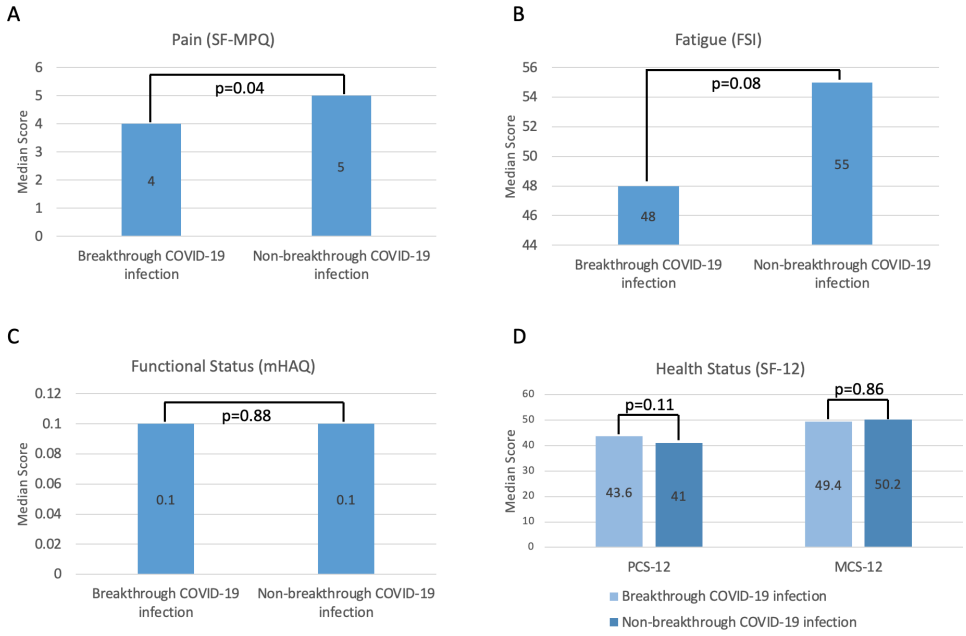

Figure 3 Patient-reported outcomes among those with breakthrough and non-breakthrough COVID-19 infection. FSI, Fatigue Symptom Inventory; mHAQ, modified Health Assessment Questionnaire; MCS-12, Mental Component Summary-12; PCS-12, Physical Component Summary-12; SF-12, 12-item Short-Form Health Survey; SF-MPQ, SF McGill Pain Questionnaire.

have suggested that severity of COVID-19 is not intrinsically lower with Omicron versus earlier variants and that differences in severity are likely due to rates of vaccination and immunity from prior infection.[36] However, other studies have shown that the Omicron variants lead to more mild infections with reduced risk of hospitalisation, mechanical ventilation and death, so it is possible that our findings may be due to intrinsic differences in PASC risk from different SARS-CoV-2 variants.[37–39] Because of the high rates of early vaccination among patients with SARDs, we are unable to compare the rates of PASC among those with and without breakthrough infection during time periods characterised by the predominance of a single SARS-CoV-2 variant; future studies evaluating differences in PASC by vaccination status while a single variant is dominant may help to elucidate this. Other improvements during the pandemic, such as outpatient treatment, may also impact our findings, though our results remained consistent in sensitivity analyses excluding these patients.

Importantly, PASC remained relatively common (41% with symptoms lasting ≥28 days) among those with breakthrough infection, highlighting the ongoing need to better understand the aetiology of PASC in patients with SARD and to identify

Table 4 Patient-reported outcomes in rheumatic disease patients following COVID-19 infection

	All rheumatic disease patients (N=280)	Breakthrough COVID-19 infection (N=116)	Non-breakthrough COVID-19 infection (N=164)	P value
Pain (SF-MPQ)				
N	258	111	147	
Median score (IQR)	4 (2–10)	4 (1–8)	5 (3–10)	0.04
Pain rating index ordinal category, n (%)				0.20
No pain	41 (15)	17 (15)	24 (15)	
Mild pain	86 (31)	43 (37)	43 (26)	
Discomforting, distressing, horrible, or excruciating pain	135 (48)	51 (44)	84 (51)	
Fatigue (FSI)				
N	264	111	153	
Median score (IQR)	54 (26–82)	48 (21–79)	55 (28–84)	0.08
Functional status (mHAQ)				
N	270	112	158	
Median score (IQR)	0.1 (0.0–0.5)	0.1 (0.0–0.5)	0.1 (0.0–0.5)	0.88
Categorical score, n (%)				0.61
Normal (<0.3)	163 (58)	70 (60)	93 (57)	
Mild, moderate, or severe (0.3 to >1.8)	107 (38)	42 (36)	65 (40)	
Health status (SF-12)				
PCS-12 score, median (IQR)	42.1 (33.0–50.8)	43.6 (33.7–52.6)	41.0 (32.2–49.5)	0.11
MCS-12 score, median (IQR)	46.8 (36.9–54.4)	49.3 (41.4–55.6)	50.2 (37.9–57.0)	0.86

FSI, Fatigue Symptom Inventory; MCS-12, Mental Component Summary score; mHAQ, modified Health Assessment Questionnaire; PCS-12, Physical Component Summary score; SF-12, 12-item Short-Form Health Survey; SF-MPQ, SF McGill Pain Questionnaire.

effective treatments for PASC. Further, the severity of PASC, as measured by validated assessments of fatigue, pain, disability and health-related quality of life of those with PASC, was similar regardless of whether it was associated with a breakthrough or a non-breakthrough infection. The aetiology of PASC remains unknown but several factors have been hypothesised to influence risk, including alterations in inflammatory cytokine profiles, cellular immune responses, reactivation of chronic viral infections and autoantibody formation.[40–46] Vaccination may reduce the risk of PASC by shortening the duration of viraemia, reducing the risk of severe COVID-19 and the associated hyperinflammatory state, influencing the cellular immune response to acute infection, among other possible explanations. It is unclear whether the risk of PASC may increase with increasing time since vaccination; our study did not have sufficient power to address this question but it should be investigated further in future studies.

Our study has several strengths. First, we used a systematic approach to identify patients with a prevalent diagnosis of a SARD at the time of SARS-CoV-2 infection. Second, we prospectively enrolled patients in RheumCARD to assess symptom duration and vaccination status, collecting patient-reported outcomes unavailable from EHR data. Third, we used two complementary definitions of PASC and conducted multiple sensitivity analyses to confirm the robustness of our findings.

Despite these strengths, our study has certain limitations. First, this study was conducted among participants who receive their care at MGB, which may limit generalisability to more diverse populations. Not all people invited to participate in RheumCARD completed a survey, but this should not affect our primary findings with regard to the risk of PASC among those who were or were not vaccinated prior to the acute infection. The proportion of current smokers was also low in our cohort; while consistent with prior estimates from similar populations, this may be a reflection of the type of patients who chose to participate. Second, the time between COVID-19 infection and survey completion was shorter among those with breakthrough infection because of the timing of the initiation of RheumCARD. While this could introduce recall bias whereby those with a non-breakthrough infection reported a longer duration of symptoms, we do not have reason to suspect this is likely. Further, our findings were similar in a sensitivity analysis where we limited the analysis to those who completed the surveys within 6 months of their index date. Also, similar proportions of patients in each group recalled flares of their underlying SARD following COVID-19 infection, suggesting no significant differential recall bias according to vaccination status. Third, some patients in the breakthrough group also received antiviral and other COVID-19 treatments which could impact our findings. However, in sensitivity analyses, we found that our observed trends persisted despite accounting for these differences. Fourth, based on the timing of infection, the variants most prevalent in those with breakthrough infections were Delta and Omicron. Due to the high vaccination rate in our cohort once vaccines became available, we are unable to compare those with and without breakthrough infection with the same SARS-CoV-2 variant. Fifth, while we used the currently accepted research definitions of PASC, it is possible that the patient reports could reflect underlying SARD activity, organ damage or be otherwise unrelated to COVID-19 resulting in overestimation of people truly experiencing prolonged COVID-19 symptoms. Future studies are needed to determine whether more homogeneous PASC subtypes may be present and to elucidate pathogenesis and possible treatments. Last, there are other PASC of varying severity including thrombotic manifestations, neuropathy, cognitive dysfunction and others (sometimes referred to as 'Long COVID-19') that were not evaluated in this study; future studies could evaluate whether these are impacted by vaccination status, anticoagulant use, comorbidity burden and other factors.

In conclusion, we found that patients with SARDs have shorter duration of COVID-19 symptoms and are less likely to have PASC at both 28 and 90 days if they are fully vaccinated prior to acute infection. These findings suggest that despite a higher risk of breakthrough infection, vaccination in patients with SARDs not only reduces the risk of severe acute outcomes but also long-term outcomes. Nonetheless, PASC remains common among patients with SARD, even after vaccination, and when present, the severity is similar to those who were either unvaccinated or partially vaccinated. Additional investigation is needed to determine the aetiology and effective treatments of PASC in SARDs.

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Contributors NJP, JAS and ZSW had access to the study data, developed the figures and tables and vouch for the data and analyses. XF and YZ performed the statistical analyses and contributed to data quality control, data analysis and interpretation of the data. CC, KV, XF, XW, YK, GQ, SS, EPB, EK and KB contributed to data collection, data analysis and interpretation of the data. ZSW and JAS directed the work, designed the data collection methods, contributed to data collection, data analysis and interpretation of the data and had final responsibility for the decision to submit for publication. All authors contributed intellectual content during the draft and revision of the work and approved the final version to be published. ZSW accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish. JAS and ZSW contributed equally as last authors. ZSW assumes overall responsibility for the content as the guarantor.

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