**Correlates of Breakthrough COVID-19 in Vaccinated Patients with Systemic Sclerosis: Survival Analysis from a Multicentre International Patient-Reported Survey**

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**Running Title** – Breakthrough COVID-19 infection in vaccinated SSc patients

**Acknowledgments:**

The authors are grateful to all respondents for completing the questionnaire. The authors also thank the Myositis Association, Myositis India, Myositis UK, Myositis Support and Understanding, the Myositis Global Network, Deutsche Gesellschaft für Muskelkranke e.V. (DGM), Dutch and Swedish Myositis patient support groups, Cure JM, Cure IBM, Sjögren’s India Foundation, Patients Engage, Scleroderma India, Lupus UK, Lupus Sweden, Emirates Arthritis Foundation, EULAR PARE, ArLAR research group, AAAA patient group, Myositis Association of Australia, APLAR myositis special interest group, Thai Rheumatism association, PANLAR, AFLAR NRAS, Anti-Synthetase Syndrome support group, and various other patient support groups and organizations for their contribution to the dissemination of this survey. Finally, the authors wish to thank all members of the COVAD study group for their invaluable role in the data collection.

**COVAD Study Group Authors**: Bhupen Barman, Yogesh Preet Singh, Rajiv Ranjan, Avinash Jain, Sapan C Pandya, Rakesh Kumar Pilania, Aman Sharma, Manesh Manoj M, Vikas Gupta, Chengappa G Kavadichanda, Pradeepta Sekhar Patro, Sajal Ajmani, Sanat Phatak, Rudra Prosad Goswami, Abhra Chandra Chowdhury, Ashish Jacob Mathew, Padnamabha Shenoy, Ajay Asranna, Keerthi Talari Bommakanti, Anuj Shukla, Arunkumar R Pande, Kunal Chandwar, Döndü Üsküdar Cansu, , Chris Wincup, Nicoletta Del Papa, Gianluca Sambataro, Atzeni Fabiola, Marcello Govoni, Simone Parisi, Elena Bartoloni Bocci, Gian Domenico Sebastiani, Enrico Fusaro, Marco Sebastiani, Luca Quartuccio, Franco Franceschini, Pier Paolo Sainaghi, Giovanni Orsolini, Rossella De Angelis, Maria Giovanna Danielli, Vincenzo Venerito, Lisa S Traboco, Jorge Rojas Serrano, Ignacio García-De La Torre, Erick Adrian Zamora Tehozol, Jesús Loarce-Martos, Sergio Prieto-González, Albert Gil-Vila, Raquel Aranega Gonzalez, Akira Yoshida, Ran Nakashima, Shinji Sato, Naoki Kimura, Yuko Kaneko, Stylianos Tomaras, Margarita Aleksandrovna Gromova, Or Aharonov, Ihsane Hmamouchi, Leonardo Santos Hoff, Margherita Giannini, François Maurier, Julien Campagne, Alain Meyer, Melinda Nagy-Vincze, Daman Langguth, Vidya Limaye, Merrilee Needham, Nilesh Srivastav, Marie Hudson, Océane Landon-Cardinal, Syahrul Sazliyana Shaharir, Wilmer Gerardo Rojas Zuleta, José António Pereira Silva, João Eurico Fonseca, Olena Zimba

**Declarations**

HC is supported by the National Institution for Health Research Manchester Biomedical Research Centre Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

**Conflicts of Interest/Competing interests:**

ALT has received honoraria for advisory boards and speaking for Abbvie, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB.

EN has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, and Lilly, and holds research grants from Pfizer and Lilly.

HC has received grant support from Eli Lilly and UCB, consulting fees from Novartis, Eli Lilly,

Orphazyme, Astra Zeneca, speaker for UCB, and Biogen.

IP has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals,

Novartis and F. Hoffmann-La Roche AG.

JBL has received speaker honoraria/participated in advisory boards for Sanofi Genzyme, Roche, and

Biogen. None is related to this manuscript.

JD has received research funding from CSL Limited.

JDP has undertaken consultancy work and/or received speaker honoraria from Astra Zenaca, Boehringer Ingelgheim, Sojournix Pharma, Permeatus Inc, Janssen and IsoMab Pharmacueticals.

MK has received speaker honoraria/participated in advisory boards for Abbvie, Asahi-Kasei, Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai, Corbus, Eisai, GSK, Horizon, Kissei, BML, Mochida, Nippon Shinyaku, Ono Pharmaceuticals, Tanabe-Mitsubishi.

NZ has received speaker fees, advisory board fees, and research grants from Pfizer, Roche, Abbvie, EliLilly, NewBridge, Sanofi-Aventis, Boehringer Ingelheim, Janssen, and Pierre Fabre; none are related to this manuscript.

TV has received speaker honoraria from Pfizer and AstraZeneca

OD has consultancy relationships with and/or has received research funding from or has served as a

speaker for the following companies in the area of potential treatments for systemic sclerosis and its

complications in the last three years: Abbvie, Acceleron, Alcimed, Amgen, AnaMar, Arxx, Baecon,

Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos, Glenmark, GSK,

Horizon (Curzion), Inventiva, iQvia, Kymera, Lupin, Medac, Medscape, Mitsubishi Tanabe, Novartis,

Roche, Roivant, Sanofi, Serodapharm, Topadur and UCB. Patent issued “mir-29 for the treatment of

systemic sclerosis” (US8247389, EP2331143).

RA has a consultancy relationship with and/or has received research funding from the following companies: Bristol Myers-Squibb, Pfizer, Genentech, Octapharma, CSL Behring, Mallinckrodt, AstraZeneca, Corbus, Kezar, Abbvie, Janssen, Kyverna Alexion, Argenx, Q32, EMD-Serono, Boehringer Ingelheim, Roivant, Merck, Galapagos, Actigraph, Scipher, Horizon Therepeutics, Teva, Beigene, ANI Pharmaceuticals, Biogen, Nuvig, Capella Bioscience, and CabalettaBio.

**Ethical approval:** Ethical approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226014 on 08-06-2021 (IEC Code: 2021-143-IP-EXP-39).

**Contribution of authors:**

Conceptualization: SA, AM, LG, and VA. Data curation: All authors. Formal analysis: SA; Funding acquisition: N/A. Investigation: LG, VA, AM, and SA. Methodology: LG, VA, and NR; Software: LG. Validation: VA, RA, LG, and HC. Visualization: RA, VA, and LG. Writing-original draft: SA, AM, and LG. Writing-review and editing: all authors. All authors take full responsibility for the integrity and accuracy of all aspects of the work.

**Disclaimer:** No part of this manuscript has been copied or published elsewhere either in whole or in part.

**Data Availability Statement:** The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

**Funding:** No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

**Introduction**

The best method of protection against COVID-19 is vaccination. There are now adequate data to show that vaccination provides good protection even in patients with systemic autoimmune rheumatic diseases (AIRDs), although serological responses may be slightly lower than those in healthy people[1]. However, in the majority of the cohorts, outcomes of connective tissue disorders have been lumped together with those of inflammatory arthritis[2–4]. This makes it difficult to interpret the effects of vaccination in less common multisystem diseases such as systemic sclerosis (SSc), where an immunosuppressed state is complicated by significant coexistent cardiopulmonary comorbidity[5].

SSc differs from other connective tissue disorders in that the inflammatory aspect is often subclinical[6]. However, it has prominent vasculopathy that may be synergistic with the prothrombotic nature of SARS-CoV-2 infection[7, 8]. There is evidence of increased COVID-19 related mortality in SSc, the most important risk factor being SSc-related interstitial lung disease[9].

There is limited data on the efficacy of vaccination for SSc. Secondary data collated from different publications seem to show that patients with SSc are not more likely to get COVID-19 [10]. [11]. A survey of approximately 100 patients with SSc showed higher vaccine hesitancy than patients with other rheumatic diseases[12]. One survey of the Scleroderma Patient-centered Intervention Network showed that vaccination is safe in patients with SSc, with no additional risk of adverse reactions or disease flare. However, information on BI following COVID19 vaccination in patients with SSc is limited. Similarly, it is not known whether the correlates of protection in SSc are different from those in other connective tissue disorders or healthy controls (HCs).

This study aimed to compare the frequency, severity, outcomes, and clinical correlates of COVID-19 infection post-vaccination in patients with SSc, other AIRDs, and HCs.

**Methods**

*Study design and data collection*

The COVID-19 Vaccination in Autoimmune Diseases (COVAD) survey used a validated questionnaire after translation into 18 different languages. It was carried out on the internet using a standard platform (Surveymonkey.com). The link to the survey was circulated by 106 physicians and associated patient support groups across 94 countries, and disseminated over social media platforms. Informed consent for participation for individuals above 18 years, was obtained through an initial question embedded in the online survey, before proceeding with the questionnaire. Incentives were not offered to complete the survey. Ethical approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, India on 08-06-2021 (IEC Code: 2021-143-IP-EXP-39). Checklist for Reporting Results of Internet E-Surveys was adhered to while the reporting results [13, 14].

The COVAD survey consisted of 36 questions aimed at assessing demographics, details of their underlying AIRDs, current medication, disease status, details of past COVID-19 including symptoms, duration and complications (hospitalization and requirement for oxygen), details of COVID-19 vaccines received, any post-vaccination adverse effects (based on the Centre for Disease Control, CDC - criteria) within seven days of vaccination, and patient-reported outcome measures as per the Patient-Reported Outcomes Measurement Information System (PROMIS) tool [15]. Duplicates were removed manually. Additional details regarding the COVAD study protocol have been published previously [16].

The survey was started on June 21, 2021, and data were retrieved for analysis after the closure of the survey on December 31, 2021. Respondents with incomplete survey responses and those who reported not taking any vaccine were excluded from the analysis. Those with prior COVID-19 infection were also excluded from the current analysis to prevent confounding by a hybrid immune effect [17].

BI was defined according to the CDC definition as a positive COVID-19 test 14 days or more after completing all recommended doses of that specific vaccine[18]. For vaccines that require two doses (Pfizer-BioNTech, two doses, three weeks apart; Oxford/Astra Zeneca ChAdOx1, 12 weeks apart; Moderna, four weeks; Covishield, 12 weeks, Covaxin, four weeks, Sinopharm, four weeks, Sputnik 12 weeks and Novovax, three weeks), the start was taken two weeks after the second dose, whereas for vaccines that required only a single dose (Janssen) it was considered two weeks after the first and only dose.

**Statistical analysis:**

The normality of the data was confirmed using the Shapiro-Wilk test. Categorical variables are presented as frequencies and proportions. The frequency of BI, symptoms, duration of illness, and severity (requiring hospitalization or supplementary oxygen) were compared between groups using independent sample t-tests and χ2 tests.

Survival analysis was performed using Kaplan-Meier curves for visualization and log-rank test for univariate analysis. A multivariate analysis was performed using Cox proportional regression to assess the correlates of protection from BI. The Cox model included age, sex, ethnicity, and immunosuppressive drugs administered at the time of vaccination.

All analyses were carried out using R software version3.5.3 (R Core Team, 2020) using various libraries including Rcpp, rstatix, dplyr, survival, survminer, ggplot2, ggpubr,, and their dependencies.

**Results:**

Of the 16,328 total respondents to the survey, 2,562 with incomplete survey responses and 2,866 who had not received a single dose of any COVID-19 vaccine were excluded. 4062 respondents who had not completed the full vaccine dosing protocol (as per the respective vaccine administered) were also excluded. A total of 6836 respondents were included in the analysis, of whom there were 427 (6.2%) patients with SSc, 2934 (42.9%) with other AIRDs, and 3475 (50.8%) HCs.

The mean age of the cohort was 44.8 (8.9), and 4991 (73.4%) were females. The respondents were from 96 different countries with the most common being 1160 Turkey (16.9%), 828 the United Kingdom (12.1%), and 752 India (11.0%). Out of the other AIRDs, the most common was rheumatoid arthritis (n=939) followed by idiopathic inflammatory myopathies (n=416), and systemic lupus erythematosus (n=371). The most commonly used vaccines were Pfizer-BioNTech (2917), Sinopharm (n=1315), and Oxford/Astra Zeneca ChAdOx1 (n=784).

The incidence of BI in SSc was lower than in HCs but comparable to that in non-SSc AIRDs (Figure 1). Patients with SSc had a lower risk for BI (HR: 0.56 (95%CI: 0.46-0.74). BIs were associated with age [HR: 0.98 (0.97-0.98)], but not ethnicity or immunosuppressive drugs at the time of vaccination (Figure 2).

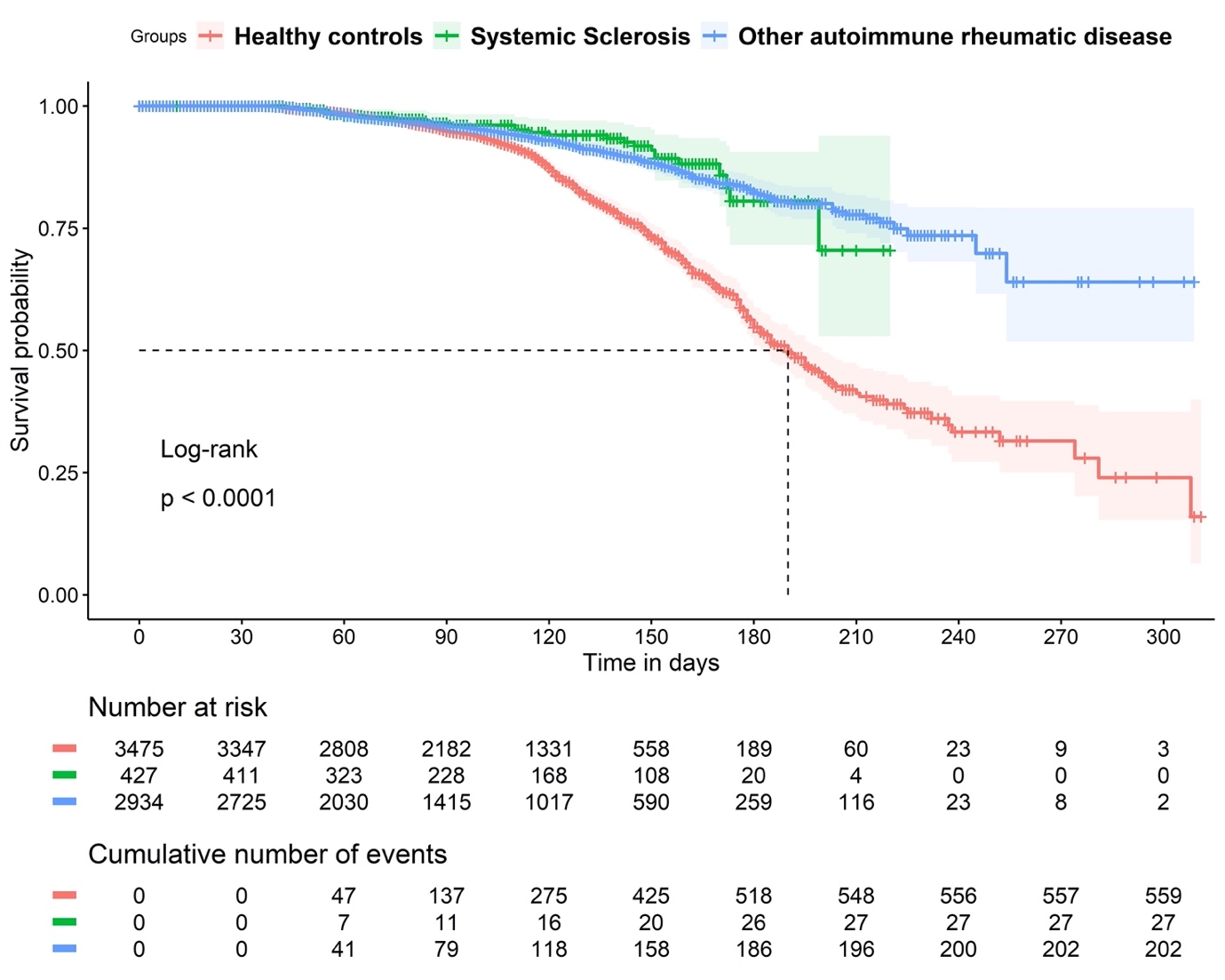


Figure 1. Survival plot versus health controls and patients with autoimmune rheumatic diseases

Table

Description automatically generated

Figure 2. Hazard ratios cox regression

BI was reported in 27 (6.3%) of patients with SSc, 202 (6.9%) of patients with non-SSc AIRDs, and 560 (16.1%) HCs during a median follow-up of 100 (IQR: 60-137) days after the first dose of vaccination. In patients with SSc, at least one-fifth were asymptomatic, and the most common symptoms were fatigue, fever, cough and headache. The BI symptoms in the three groups are summarized in Table 1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Systemic sclerosis | Healthy controls | Other (non SSc) AIRDs | p-value |
| Asymptomatic | 6 (22.2) | 49 (8.8) | 16 (7.9) | 0.047 |
| Fever | 14 (51.8) | 275 (49.1) | 121 (59.9) | 0.031 |
| Fatigue | 18 (66.7) | 397 (70.9) | 150 (74.3) | 0.56 |
| Muscle aches | 15 (55.6) | 319 (57.0) | 112 (55.4) | 0.93 |
| Cough | 12 (44.4) | 236 (42.1) | 90 (44.5) | 0.83 |
| Breathlessness | 9 (33.3) | 116 (20.7) | 67 (33.2) | 0.00 |
| Chest pain | 5 (18.5) | 85 (15.2) | 45 (22.3) | 0.07 |
| Diarrhoea | 6 (22.2) | 103 (18.4) | 49 (24.3) | 0.19 |
| Nausea/vomiting | 4 (14.8) | 60 (10.7) | 28 (13.9) | 0.43 |
| Headache | 12 (44.4) | 289 (51.6) | 105 (52.0) | 0.75 |
| Skin rashes | 0 | 26 (4.6) | 14 (6.9) | 0.21 |
| Joint pains | 9 (33.3) | 195 (34.8) | 72 (35.6) | 0.96 |

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The mean duration of symptomatic disease in patients with SSc was 16.5 (19.5) days, which was comparable to HCs: 14.4 (18.6%). However, it was significantly longer in case of non-SSc AIRD group [20.8 (25.2) days]. Hospitalization [SSc: 4 (14.8%); HCs: 37 (6.6%); non-SSc AIRDs: 32 (15.8%)] and the need for oxygenation [SSc: 1 (25.0%); HCs: 17 (45.9%); non SSc AIRDs: 13 (40.6%)] were not statistically different between the groups.

**Discussion:**

Preliminary data on COVID-19 in patients with AIRDs showed that the use of moderate to high doses of glucocorticoids, but not the underlying AIRDs, predicted more severe disease[2]. Multiple cohorts around the world have shown that vaccination is safe in patients with AIRDs [19–22]. A previous survey reported that the incidence of BI in patients with AIRDs was approximately 1.7% in fully vaccinated patients[23]. Our analysis showed an incidence of 6.3% with a much higher incidence in HCs.

In our study, the incidence of BI in SSc and other AIRDs was statistically similar, implying that SSc per se does not predispose individuals to BI. The lower incidence of BI in SSc and other AIRDs is best explained by a shielding effect with heightened awareness [24]. Those with chronic illnesses are more likely to follow COVID-19 protection protocols such as masking, physical distancing, and social distancing. This has been shown in other AIRDs, such as rheumatoid arthritis, where there is increased risk perception leading to strict shielding [25].

Regarding symptom severity, there appeared to be more patients with asymptomatic infection and breathlessness. The higher number of asymptomatic patients may be explained by the greater awareness of patients after exposure to a potential case of COVID-19. Patients with non-SSc AIRDs also had similar rates of asymptomatic infections. Higher breathlessness may be due to underlying interstitial lung disease or other comorbidities [26].

In the multivariate Cox analysis, even after controlling for other variables, patients with SSc or other AIRDs had a much lower HR for BI than the HCs. Age is a determinant of BI. Immunosenescence with impaired interferon and antibody responses can increase the risk of BI with advancing age [27, 28]. Ethnicity also did not influence the risk of infection; although Hispanics and indigenous American/Pacific islanders had numerically high HR, the confidence interval was wide and thus, not statistically significant.

Immunosuppressants administered at the time of vaccination did not influence the risk of BI. Overall, in the cohort of SSc, 110 reported to have received mycophenolate, 7 rituximab and 5 cyclophosphamide. This may indicate a relatively lower utilization of cyclophosphamide or rituximab in SSc-ILD in the responders of the survey or patients with a more severe ILD or high global disease burden may not have participated in the study. Previous studies have shown that higher doses of glucocorticoids and certain drugs lead to lower post-vaccination antibody titres[2, 4, 29]. It is possibly that the effect size of these drugs is not large enough to influence susceptibility to BI, because they will have more resistance to infection than a vaccine-naïve population.

The COVAD international survey was designed to collate adverse effects related to COVID-19 vaccination, BI and correlates of protection against BI[30]. This has helped uncover the risk of adverse effects and BI in individual rheumatic diseases, such as rheumatoid arthritis[31], systemic lupus erythematosus[32], and idiopathic inflammatory myopathies[33, 34]. Previously, the adverse effects of vaccination in SSc patients in the COVAD survey have been described[35]. Similarly, the current analysis showed that the risk of BI in SSc was not different from than in other ARDs.

Strengths and Limitations

The major strength of this study is the large number of patients with SSc. There were also a good number of patients with other AIRDs and HCs. This was a global cohort from 94 countries with representative samples from different continents, ethnicity, and even relative proportions of AIRDs. In addition, we only included participants fulfilling the definition of being fully vaccinated, as provided by the CDC.

Convenience sampling was used as a self-reported survey. There can be minor misclassifications of underlying diseases, medications used, or definitive COVID-19. However, a large number of participants nullify the effects of minor misclassification. Again, there is a selection bias as it was not fully representative, since it was an online-only survey. Patients from disadvantaged backgrounds, who may potentially have more BI, may have been missed. Patients with severe BI that resulted in death or associated complications were excluded. Additionally, we did not capture information related to cumulative dose of immunosuppressive medications, glucocorticoids and co-morbidities such as ILD, which might have influenced the BI.

~~Due to differences in screening and treatment protocols between countries, patient reported information on comorbidities such as ILD may be heterogenous. Thus, information on such comorbidities were not collected and this remains another limitation.~~ In addition, the survey did not capture organ dysfunction during BI or any post-infection sequelae such as long-COVID syndrome.

**Conclusion**

BI occurred in 6.3% of patients with SSc who had been completely vaccinated with any of the WHO recognised vaccines. The risk for BI in patients with SSc was similar to those with non-SSc AIRD but similar to that of healthy controls. The severity of BI was similar between groups. Only age was associated with BI while ethnicity and the class of immunosuppressive medications were not.

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