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Arthritis Care & Research
Vol. 76, No. 1, January 2024, pp 88–97
DOI 10.1002/acr.25226

American College of Rheumatology
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Does the Impact of COVID-19 on Patients With Systemic Sclerosis Change Over Time?

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Objective. The outcome of patients with COVID-19 improved over the pandemic, including patients with systemic rheumatic diseases. However, data on patients with systemic sclerosis (SSc) are lacking. This study aimed to assess the outcome of patients with both SSc and COVID-19 over several waves.

Methods. Patients with both SSc and COVID-19 who were registered in the European Scleroderma Trials and Research group (EUSTAR) were collected between April 2020 and April 2021. Patients were assigned to waves 1, 2, or 3 depending on the date of their COVID-19 diagnosis. Primary endpoints were death, intensive care unit stay, or ventilatory support (severe outcome). Subgroup analyses of patients who were hospitalized or died were conducted. General and SSc-specific characteristics and treatment were compared over the waves. Descriptive statistics and multivariate logistic regression were applied.

Results. A total of 333 patients were included; 57 patients (17%) had a severe outcome, and 30 patients (9%) died. Compared to wave 1, significantly fewer patients with SSc suffered from severe COVID-19 in waves 2 and 3 (28.2% vs 9.8% and 12.7%; $P < 0.001$), fewer patients required hospitalization (46.7% vs 19.6% and 25.5%; $P < 0.001$) or ventilatory support (24.0% vs 8.7% and 10.9%; $P = 0.001$), and fewer patients died (15.7% vs 5.0% and 7.5%; $P = 0.011$). Patients were significantly younger, more often men, had less frequent arterial hypertension, and less SSc cardiac involvement over waves 1 to 3. Patients received significantly less medium to high doses of corticosteroids as they did SSc treatment.

Conclusion. The outcome of patients with both SSc and COVID-19 improved significantly over time because of intrinsic and extrinsic factors.

INTRODUCTION

Over more than three years, the SARS-CoV-2 pandemic has strongly impacted the whole world.[1] More than 630 million cases of infections and 6.6 million deaths have been reported.[2] Not only is modern medicine being challenged to develop novel treatment options[3] but also to gain experience in epidemiologic and pathophysiologic characteristics of SARS-CoV-2,[4] as well as to

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SIGNIFICANCE & INNOVATIONS

- Our study compares outcome due to COVID-19 in patients with systemic sclerosis (SSc) over the different waves, ensuring a broad generalizability of our results.
- This is the first study to report improved outcome of patients with both SSc and COVID-19 in a multicenter international SSc cohort.
- The results reflect the implementation of the most current treatment and management guidelines, including handling of immunosuppressive treatment.
- Our data support the assumption that following these adapted treatments and management guidelines results in a better outcome for patients with both SSc and COVID-19.

discover which patients are at highest risk for a worse outcome.[5] Major research projects have been conducted or are ongoing to study the course of COVID-19 in different diseases, including systemic sclerosis (SSc).[6–8]

SSc is a multiorgan autoimmune disease with high morbidity and mortality and frequent organ manifestations, including interstitial lung disease (ILD).[9–12] Many patients receive immunosuppressive treatment, which has been shown to impact the outcome of COVID-19 infection.[13,14] As demonstrated recently, patients with SSc are at risk for a more severe COVID-19 disease course.[13,15] Multiple common risk factors are known to have a relevant impact on the outcome of COVID-19 in the general population, such as older age, male sex, and comorbidities like cardiovascular disease.[16,17] SSc-related disease characteristics, such as the presence of ILD, pulmonary arterial hypertension (PAH), and SSc-associated renal or cardiac disease were associated with hospitalization and more severe outcomes.[13] These analyses were conducted over a time span from December 2019 to February 2021, but the specific time period of SARS-CoV-2 mutations were not taken into account. This is important, because multiple SARS-CoV-2 mutations have occurred over these years, resulting in substantial differences in the clinical course of COVID-19. In a population-wide study in the UK, a relevant risk reduction for mortality in hospitalized patients was shown in wave 2 (starting October 2020) compared to wave 1 (starting March 2020).[6] In patients with systemic autoimmune rheumatic diseases (SARD), a study from the US showed a decline of severe outcomes in patients with SARD over the first months of the pandemic.[7] Furthermore, a recent publication from Boston verified a 71% risk reduction of hospitalization or death

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Additional supplementary information cited in this article can be found online in the Supporting Information section http://onlinelibrary.wiley.com/doi/10.1002/acr.25226.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25226.

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Submitted for publication March 31, 2023; accepted in revised form August 24, 2023.

with the Omicron variant compared to early waves in patients with SARD.[8] A subgroup analysis of the 35 patients with SSc included in that study was not performed.

Additionally, because of increasing knowledge about SARS-CoV-2 mutations and outcome of patients on certain immunosuppressants,[18,19] physicians were able to adapt patient management. On the one hand, this included avoidance of certain immunosuppressants, but on the other hand, an awareness of keeping patients on their immunosuppressive treatment for better control of SSc organ manifestations developed. This is mirrored in the updated European Alliance of Associations for Rheumatology (EULAR) guidelines for the management of patients with rheumatic diseases in the context of SARS-CoV-2, with the recommendation to postpone the next rituximab (RTX) cycle as well as to continue glucocorticoids with the lowest possible dose, whereas other immunosuppressants were recommended to be continued unchanged.[20] Furthermore, different treatments used in rheumatic diseases, such as hydroxychloroquine and tocilizumab, were tested for the treatment of SARS-CoV-2 infection, which again influenced treatment patterns for patients with SARD.[21]

A change of disease course over the waves may be expected in patients with SSc—secondary to internal (the virus mutations) and external (change of patient management) influence—but has so far not been studied. Therefore, the aim of our study was to determine the disease outcome of COVID-19 in patients with SSc over time.

PATIENTS AND METHODS

Patients with SSc from the European Scleroderma Trials and Research (EUSTAR) cohort. Patients with prospectively collected and standardized data from EUSTAR, a registry of patients with SSc containing data on COVID-19, were included. Data collection of patients with both SSc and COVID-19 was started in the EUSTAR database on April 8, 2020, and completed on April 15, 2021. General characteristics and SSc-specific information at the time of COVID-19 infection were collected and are detailed below. Characteristics specific for COVID-19, such as hospitalization, duration of hospitalization, intensive care unit (ICU) admission, any ventilatory support, and death, were recorded, as was drug therapy for SSc and COVID-19. The time from COVID-19 to outcome assessment was recorded in the EUSTAR COVID database as total duration from symptom onset to outcome. Inclusion required pre-existing SSc and a confirmed or presumptive diagnosis of COVID-19 regardless of whether COVID-19 was diagnosed by classical symptoms and contact to SARS-CoV-2 only or confirmed by polymerase chain reaction (PCR). The EUSTAR data collection was approved by local and national ethical committees and the COVID-19 module within the EUSTAR database was approved by the Oslo University Hospital Data Protection Office.

SARS-CoV-2 infections. To make patients from different geographical regions and date of COVID-19 onset comparable to each other, we grouped all patients into waves from 1 to 4. These were determined for each country using the COVID-19 dashboard of the Center for Systems Science and Engineering at Johns Hopkins University.[22] The cutoff point was the lowest number of weekly cases between two visually apparent waves, whereas the week with the lowest incidence number was added to the previous wave. Countries included Belgium, Brazil, the Czech Republic, France, Germany, Greece, Hungary, Iran, Israel, Italy, Japan, The Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Switzerland, Turkey, UK, and US (Supplementary Table 1).

Assessment of general and SSc specific risk factors and treatment. We assessed the impact of general and SSc-specific risk factors and treatments as covariates for the outcome over time. General characteristics were age, sex, and comorbidities, including type 2 diabetes mellitus, arterial hypertension, cardiovascular and chronic obstructive pulmonary disease, malignancy, and smoking. We compared patients with any comorbidity and two or more comorbidities. SSc-specific risk factors included SSc subtype (diffuse or limited cutaneous SSc); disease duration (from first non-Raynaud phenomenon); organ manifestations including ILD (diagnosed by high-resolution computed tomography or x-ray); PAH (diagnosed by right heart catheterization); renal disease (including scleroderma renal crisis and SSc-related renal failure); cardiac disease (defined as any conduction blocks, high-grade arrhythmias, diastolic dysfunction, or pericardial effusion); esophageal involvement (defined as dysphagia or reflux); and musculoskeletal involvement (defined as any arthritis, muscle weakness, or muscle enzyme elevation greater than two times the upper limit of normal, tendon friction rub); digital ulcers; and modified Rodnan skin score. We also assessed the impact of immunosuppressive treatment including RTX, mycophenolate mofetil, cyclophosphamide, methotrexate (MTX), azathioprine (AZA), corticosteroids (prednisone >10 mg/day or equivalent), tocilizumab, abatacept, tacrolimus, tumor necrosis factor (TNF) inhibitors or autologous stem cell transplantation and other treatments such as antimalarials, nintedanib, and intravenous immunoglobulins. We also assessed the change in immunosuppressive treatment at the time of COVID-19 diagnosis (medication switched, dose or number of drugs reduced or stopped) and COVID-19 specific treatments (ventilatory support including any invasive or noninvasive mechanical ventilation; invasive was defined as intubation and/or extracorporal membrane oxygenation and noninvasive as any other mechanical, noninvasive ventilatory support, antivirals, antibiotics, tocilizumab, antimalarials, systemic corticosteroids, and others [colchicine, nonsteroidal anti-inflammatory drugs, heparin, aspirin, paracetamol, vitamin D and plasma exchange, interferon beta]). Analyses included receiving any of the following COVID-treatments: antivirals, antibiotics,

tocilizumab, antimalarials, or systemic corticosteroids, as well as multiple treatments, defined as more than one.

Outcome measures. First, we determined time/wave dependent changes of the following: 1) general characteristics and characteristics of patients with SSc, as described above; 2) immunosuppressive treatment in patients with both SSc and COVID-19, as defined above; 3) specific treatment for COVID-19, as defined above. Next, we assessed our primary outcome measure, which was severe outcome of COVID-19. Severe outcome was defined as hospitalization with ventilatory support (noninvasive and/or invasive mechanical ventilation) and/or ICU stay and/or death.[13] We then conducted subgroup analyses of patients who were hospitalized and/or died.

Statistical analysis. Statistical analyses were performed using the statistical software IBM SPSS version 26 and STATA version 17. Descriptive statistics were applied as appropriate, and descriptive tables were created. Continuous variables were reported as mean ± SD and categorical variables as numbers and percentages. Characteristics between the presence or absence of a severe outcome and variables across the different waves were compared using the chi-square or Fisher's exact test for categorical variables and analysis of variance with the Tukey post hoc test for continuous variables. Multivariable logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) adjusting for significant different baseline characteristics were applied using severe outcome and hospitalization as endpoints. In the multivariable analyses, 8 to 10 events per variable were needed. All multivariable analyses were preceded by an estimation of correlation between variables. Models were tested by area under the curve with 95% CI, in which values ≥0.7 were considered acceptable. $P < 0.05$ was considered significant for all analyses. Patient data for this study were extracted from the COVID-19 EUSTAR database. Data are available upon reasonable request. Data collection by the EUSTAR database was approved by local and national ethical committees, and specifically, the module of COVID-19 within EUSTAR was approved by the Oslo University Hospital Data Protection Office.

RESULTS

Patient characteristics and treatments over the waves. We included 333 of the 351 registered patients. We excluded 14 patients because of an unknown date of COVID-19 diagnosis. Of the included patients, 125 (37.5%) were assigned to wave 1, 153 (45.9%) to wave 2, and 55 (16.5%) to wave 3, respectively. Only four patients were assigned to wave 4 and was excluded from all analyses because it did not allow for any meaningful analyses. Of all the measured patients, 37 (11.2%) had COVID-19 diagnosed by symptoms only (26.6%, 2.0%, 1.8% in waves 1, 2, and 3, respectively), whereas the other 295 (88.8%) were confirmed by PCR.

Patients were significantly younger in wave 3 (49.3 years) compared to waves 1 (57.8 years; $P < 0.001$) and 2 (55.3 years; $P = 0.014$) and were more frequently men (20.8%, 14.4%, and 30.9% in waves 1, 2, and 3, respectively; $P = 0.027$), whereas fewer patients experienced arterial hypertension. There was a trend of fewer patients experiencing more than two comorbidities (Table 1).

Except for SSc cardiac disease, which showed a significantly lower frequency in later waves (44.4%, 20.3%, and 13.2% in waves 1, 2, and 3, respectively; $P < 0.001$), SSc-specific characteristics did not differ over time (Table 1). Immunosuppressive treatment patterns showed a significant decrease in the use of corticosteroids or prednisone equivalent dosed >10 mg over time (5.6%, 0.7%, and 1.8% in waves 1, 2, and 3, respectively; $P = 0.037$), and a tendency for less use of RTX (14.4%, 6.5%, and 9.1% in waves 1, 2, and 3, respectively; $P = 0.090$) (Table 2). Treatment with MTX, AZA, mycophenolate mofetil, corticosteroids or prednisone equivalent dosed <10 mg, abatacept, tacrolimus, TNF inhibitors or autologous stem cell transplantation, antimalarials and intravenous immunoglobulins was not significantly different between the waves.

The use of treatment for COVID-19 declined significantly for any COVID-19 treatment (67 [56%], 59 [39%], 13 [24%] in waves 1, 2, and 3, respectively; $P < 0.001$), multiple COVID-19 treatments (41 [44%], 33 [27%], 7 [14%] in waves 1, 2, and 3, respectively; $P = 0.001$), antibiotics (47 [39%], 51 [34%], 9 [16%] in waves 1, 2, and 3, respectively; $P = 0.011$), antimalarials (51 [43%], 6 [4%], 0 [0%] in waves 1, 2, and 3, respectively; $P < 0.001$) and tocilizumab (6 [5%], 1 [1%], 0 [0%] in waves 1, 2, and 3, respectively; $P = 0.024$), whereas the use of antivirals and systemic corticosteroids did not differ significantly across the waves.

Severe outcome decreased significantly across the different waves. Over the mean ± SD days (7.1 ± 6.4) from onset of first COVID-19 symptom, 57 out of 333 patients (17%) experienced a severe outcome. Of these patients, 14 (25%) received invasive ventilation, 45 (79%) noninvasive ventilation, 29 (51%) needed admission to the ICU, and 31 (54%) died. Severe outcome occurred in 28.2%, 9.8%, and 12.7% in waves 1, 2, and 3, respectively ($P < 0.001$). Hospitalization, death, and need for noninvasive mechanical ventilation, as well as ventilatory support, decreased significantly over time (Figure 1).

We conducted a detailed analysis of 57 patients with severe outcomes. We saw a significant decrease of SSc cardiac involvement (82.6%, 21.4%, and 42.9% in waves 1, 2, and 3, respectively; $P = 0.001$) and an increase of renal disease (8.8%, 13.3%, and 57.1%, in waves 1, 2, and 3, respectively; $P = 0.006$), as well as a trend of reduced change of immunosuppressive treatment (75.0%, 87.5%, 33.3% in waves 1, 2, and 3, respectively; $P = 0.068$) over the waves. The use of antimalarials as a COVID-19 treatment declined significantly (71.9%, 14.3%, and 0.0% in waves 1, 2, and 3, respectively; $P < 0.001$) (Tables 3 and 4).

Table 1. Patient characteristics over waves 1 to 3*

Characteristics	Number of patients with available data	All positives	Wave 1 positives	Wave 2 positives	Wave 3 positives	*P* value
Waves 1, 2, 3, n (%)	333		125 (37.5)	153 (45.9)	55 (16.5)	
General characteristics						
Age, years (SD)	328	55.3 (13.8)	57.8 (14.0)	55.3 (13.1)	49.3 (13.7)	<0.001–0.290
Male, n (%)	333	65 (19.5)	26 (20.8)	22 (14.4)	17 (30.9)	0.027
Comorbidities, n (%)	332	144 (43.4)	61 (48.8)	61 (40.1)	22 (40.0)	0.301
More than two comorbidities, n (%)	332	102 (30.7)	47 (37.6)	43 (28.3)	12 (21.8)	0.072
Arterial hypertension, n (%)	332	62 (18.7)	32 (25.6)	24 (15.8)	6 (10.9)	0.031
Cardiovascular disease, n (%)	329	40 (12.2)	17 (13.6)	17 (11.4)	6 (10.9)	0.818
Diabetes mellitus, n (%)	332	144 (43.4)	61 (48.8)	61 (40.1)	22 (40.0)	0.301
Chronic obstructive lung disease, n (%)	332	22 (6.6)	12 (9.6)	7 (4.6)	3 (5.5)	0.233
Malignancy, n (%)	144	21 (14.6)	13 (21.3)	6 (9.8)	2 (9.1)	0.146
Smoking, n (%)	133	14 (10.5)	6 (10.7)	7 (12.3)	1 (5.0)	0.658
SSc-specific characteristics						
ILD, n (%)	283	128 (45.2)	42 (40.0)	63 (48.1)	23 (48.9)	0.396
PAH, n (%)	320	30 (9.4)	16 (13.2)	11 (7.6)	3 (5.5)	0.164
Esophageal disease, n (%)	283	198 (70.0)	81 (73.6)	79 (63.7)	38 (77.6)	0.113
Renal disease, n (%)	330	16 (4.8)	4 (3.2)	8 (5.3)	4 (7.3)	0.478
Cardiac disease, n (%)	282	73 (25.9)	36 (44.4)	30 (20.3)	7 (13.2)	<0.001
dcSSc, n (%)	330	142 (43.0)	56 (44.8)	60 (40.0)	26 (47.3)	0.570
ATA positive, n (%)	320	124 (38.8)	42 (35.0)	61 (41.2)	21 (40.4)	0.563
Time between first non-Raynaud to COVID, years (SD)	301		11.70 (9.02)	9.46 (8.34)	8.72 (10.83)	0.126–0.875
Digital ulcers (ever), n (%)	328	127 (38.7)	50 (40.3)	55 (36.9)	22 (40.0)	0.828
Musculoskeletal, n (%)	328	75 (22.9)	27 (22.0)	32 (21.3)	16 (29.1)	0.480
mRSS, score (SD)	289		7.2 (7.46)	7.4 (7.27)	8.5 (7.25)	0.539–0.963

* Shown are general and systemic sclerosis (SSc) patient characteristics over waves 1 to 3. The percentages correspond to the proportion of positive patients per wave. For continuous variables, a range of *P* values is reported, because multiple comparisons were performed with the analysis of variance test. ATA, anti-topoisomerase antibody; dcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; PAH, pulmonary arterial hypertension.

A multivariable regression analysis with severe outcome as an endpoint adjusting for arterial hypertension and SSc cardiac disease, which both significantly differed over the waves (Table 1), showed that in wave 2 significantly fewer severe outcomes were seen compared to wave 1 (OR 0.37, 95% CI 0.17–0.82; $P = 0.014$). Cardiac disease had a significant association with severe outcome (OR 3.28, 95% CI 1.58–6.84; $P = 0.001$), whereas age, sex, and arterial hypertension did not impact severe outcome (Figure 2A).

Subgroup analyses of patients who died and/or were hospitalized showed differences over time. Of the 31 patients who died, significantly more patients with SSc were

Table 2. SSc treatment of patients over waves 1 to 3*

Variables	Number of patients with available data	All positives	Wave 1 positives	Wave 2 positives	Wave 3 positives	*P* value
Waves 1, 2, 3, n (%)	333		125 (37.5)	153 (45.9)	55 (16.5)	
SSc treatment						
Immunosuppressives, n (%)	333	194 (58.3)	72 (57.6)	84 (54.9)	38 (69.1)	0.184
Change in immunosuppressives, n (%)	185	108 (58.4)	44 (63.8)	44 (57.9)	20 (50.0)	0.370
RTX, n (%)	333	33 (9.9)	18 (14.4)	10 (6.5)	5 (9.1)	0.090
Mycophenolate mofetil, n (%)	333	89 (26.7)	32 (25.6)	36 (23.5)	21 (38.2)	0.102
Nintendanib, n (%)	333	7 (2.1)	1 (0.8)	3 (2.0)	3 (5.5)	0.106
Tocilizumab, n (%)	333	12 (3.6)	2 (1.6)	7 (4.6)	3 (5.5)	0.219
Corticosteroids >10 mg/d prednisone equivalent, n (%)	333	9 (2.7)	7 (5.6)	1 (0.7)	1 (1.8)	0.035

* Shown are systemic sclerosis (SSc) treatments of patients over Waves 1 to 3. The percentages correspond to the proportion of positive patients per wave. RTX, rituximab.

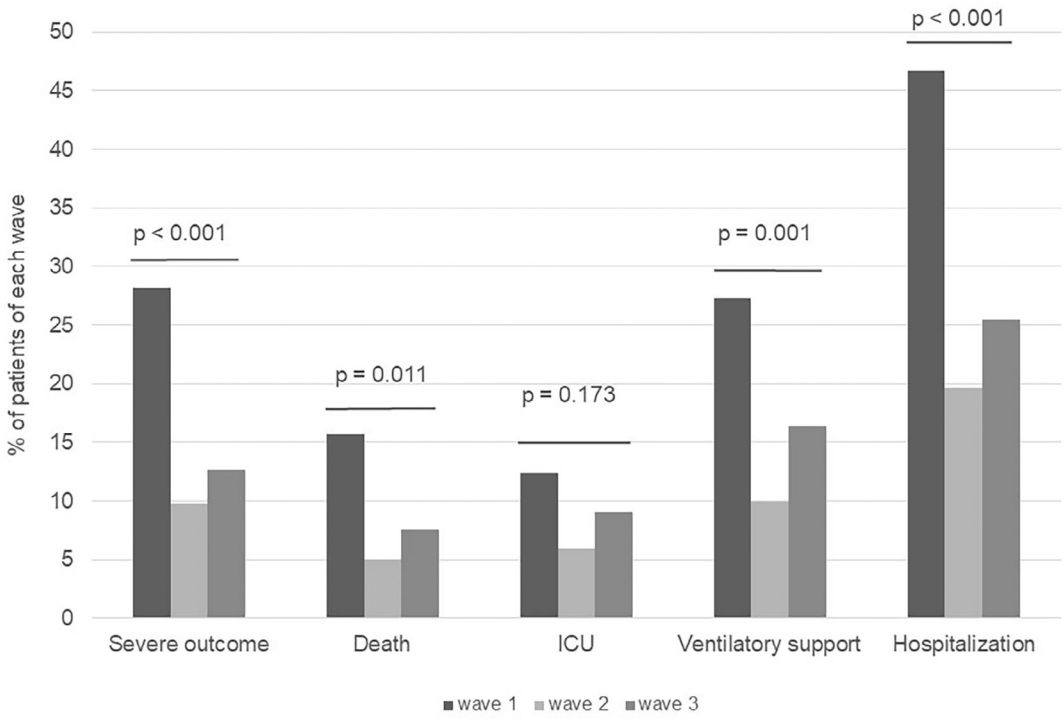

Figure 1. Different outcomes with proportion of patients of wave 1 to 3. Proportion of patients of each wave for the different outcomes. Death, intensive care unit (ICU) stay and/or ventilatory support define severe outcome; hospitalization is not included in the definition of severe outcome. Invasive and/or noninvasive mechanical support define ventilatory support.

male in wave 2 (26.3%, 85.7%, and 25.0% in wave 1, 2, and 3, respectively; P = 0.019) and only patients in wave 1 were treated with antimalarials for COVID-19 (62.5% in wave 1; P = 0.006). Five of these patients experienced SSc renal disease (5.6%, 28.6%, and 50.0% in waves 1, 2, and 3, respectively; P = 0.069) (Supplementary Tables 2 and 3).

Table 3. Patient characteristics in severe outcome over waves 1 to 3*

Characteristics	All positives	Wave 1 positives	Wave 2 positives	Wave 3 positives	*P* value
Waves 1, 2, 3, n (%)	57 (17)	35 (59.3)	15 (25.4)	7 (11.9)	
General characteristics					
Age, years (SD)	62.0 (12.8)	62.9 (11.3)	62.6 (12.8)	54.7 (19.4)	0.283–0.997
Male, n (%)	15 (26.3)	8 (22.9)	5 (33.3)	2 (28.6)	0.735
Comorbidities, n (%)	30 (52.6)	19 (54.3)	8 (53.3)	3 (42.9)	0.857
More than two comorbidities, n (%)	26 (45.6)	16 (45.7)	7 (46.7)	3 (42.9)	0.986
Arterial hypertension, n (%)	21 (36.8)	12 (34.3)	6 (40.0)	3 (42.9)	0.873
Cardiovascular disease, n (%)	13 (23.2)	8 (22.9)	3 (21.4)	2 (28.6)	0.932
SSc-specific characteristics					
ILD, n (%)	26 (56.5)	15 (55.6)	8 (61.5)	3 (50.0)	0.884
PAH, n (%)	12 (22.2)	8 (25.0)	3 (20.0)	1 (14.3)	0.802
Esophageal disease, n (%)	39 (79.6)	25 (83.3)	9 (69.2)	5 (83.3)	0.557
Renal disease, n (%)	9 (16.1)	3 (8.8)	2 (13.3)	4 (57.1)	0.006
Cardiac disease, n (%)	25 (56.8)	19 (82.6)	3 (21.4)	3 (42.9)	0.001
dcSSc, n (%)	31 (55.4)	18 (51.4)	8 (57.1)	5 (71.4)	0.616
ATA positive, n (%)	25 (47.2)	14 (43.8)	9 (64.3)	2 (28.6)	0.251
Musculoskeletal involvement, n (%)	11 (20.4)	5 (15.2)	4 (28.6)	2 (28.6)	0.490
Digital ulcers (current), n (%)	3 (7.9)	3 (11.5)	0 (0)	0 (0)	0.472
Digital ulcers (ever), n (%)	21 (37.5)	11 (32.4)	6 (40.0)	4 (57.1)	0.455
Time of first non-Raynaud SSc to COVID (SD)		11.78 (10.42)	14.54 (14.37)	17.86 (22.34)	0.528–0.858

* Shown are general and systemic sclerosis (SSc) patient characteristics of patients with severe outcome over Waves 1 to 3. The percentages correspond to the proportion of positive patients per wave. For continuous variables, a range of *P* values is reported, as multiple comparisons were performed with the analysis of variance (ANOVA) test. ATA, anti-topoisomerase antibody; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension.

Table 4. SSc and COVID treatment in severe outcome over waves 1 to 3*

Variables	All positives	Wave 1 positives	Wave 2 positives	Wave 3 positives	*P* value
Waves 1, 2, 3, n (%)	57 (17)	35 (59.3)	15 (25.4)	7 (11.9)	
SSc treatment					
Immunosuppressives, n (%)	39 (68.4)	25 (71.4)	9 (60.0)	5 (71.4)	0.716
Change in immunosuppressives, n (%)	27 (71.1)	18 (75.0)	7 (87.5)	2 (33.3)	0.068
RTX, n (%)	12 (21.1)	7 (20.0)	3 (20.0)	2 (28.6)	0.873
Mycophenolate mofetil, n (%)	18 (31.6)	14 (40.0)	4 (26.7)	0 (0)	0.103
Nintendanib, n (%)	1 (1.8)	0 (0)	1 (6.7)	0 (0)	0.241
Tocilizumab, n (%)	0	0	0	0	
Corticosteroids >10 mg/d prednisone equivalent, n (%)	3 (5.3)	2 (5.7)	1 (6.7)	0 (0)	0.794
COVID treatment					
Any COVID treatment, n (%)	46 (85.2)	28 (84.8)	12 (85.7)	6 (85.7)	0.996
Multiple COVID treatments, n (%)	36 (80.0)	23 (79.3)	9 (81.8)	4 (80.0)	0.984
Antivirals, n (%)	10 (18.9)	8 (25.0)	1 (7.1)	1 (14.3)	0.343
Antibiotics, n (%)	38 (71.7)	24 (75.0)	10 (71.4)	4 (57.1)	0.637
Systemic corticosteroids, n (%)	25 (47.2)	12 (37.5)	8 (57.1)	5 (71.4)	0.182
Antimalaria, n (%)	25 (47.2)	23 (71.9)	2 (14.3)	0 (0)	<0.001
Tocilizumab, n (%)	7 (13.5)	6 (19.4)	1 (7.1)	0 (0)	0.288

* Shown are systemic sclerosis (SSc) and COVID treatments of patients with severe outcome over waves 1 to 3. The percentages correspond to the proportion of positive patients per wave. RTX, rituximab.

Of the 101 patients who were hospitalized, 83 (82%) were due to COVID-19, 5 (5%) to SSc-related causes, and 13 (13%) due to other or unknown reasons. Significant differences were noted among the waves: patients were younger in wave 3 (54.1 years) compared to wave 2 (66.3 years; $P = 0.026$). There was less SSc cardiac involvement (59.0%, 25.0%, and 21.4% in waves 1, 2, and 3, respectively; $P = 0.005$) and generally less use of antibiotics (70.4%, 82.1%, and 42.9% in waves 1, 2, and 3, respectively; $P = 0.033$). There was successively less antimalarial use (72.2%, 7.1%, and 0.0% in waves 1, 2, and 3, respectively; $P < 0.001$) but more corticosteroids use (29.6%, 57.1%, and 64.3% in waves 1, 2, and 3, respectively; $P = 0.012$) (Supplementary Tables 4 and 5).

A multivariable regression analysis with hospitalization as the endpoint, adjusting again for arterial hypertension and SSc cardiac disease, showed that, in waves 2 and 3, significantly fewer patients with SSc were hospitalized compared to wave 1 (OR 0.26, 95% CI 0.14–0.48; $P < 0.001$ and OR 0.28, 95% CI 0.12–0.65; $P = 0.003$). None of the other baseline characteristics impacted hospitalization (Figure 2B).

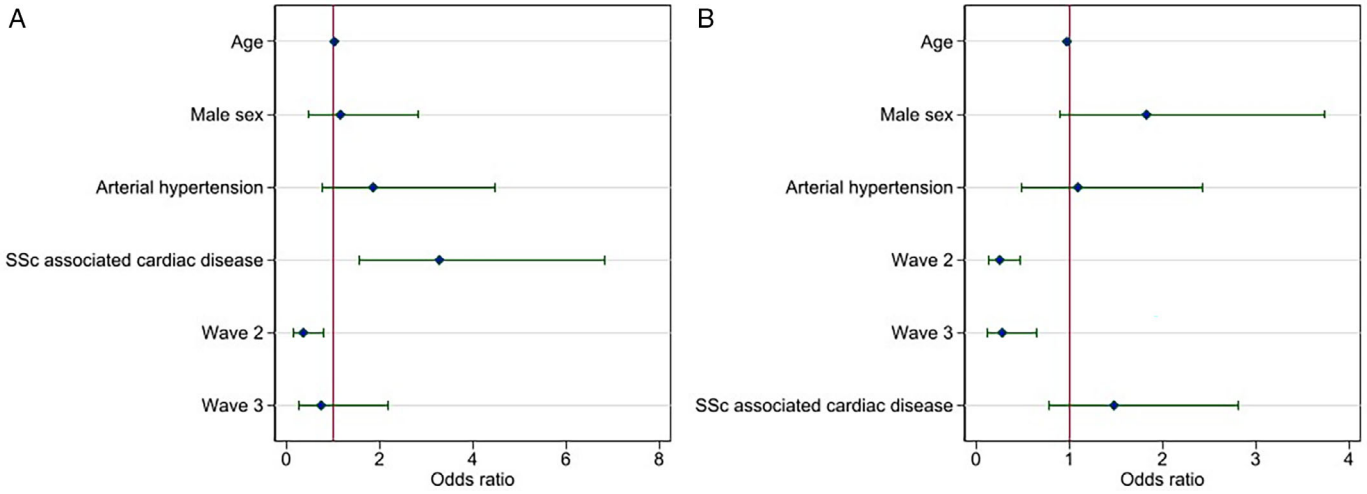

Figure 2. (**A**) Forrest plot showing associations with severe outcome over wave 2 and 3 compared to wave 1. Shown is a significant reduction of severe outcomes in wave 2 and a significant association with SSc-associated cardiac disease. Area under the curve (AUC) = 0.75. (**B**) Forrest plot showing associations with hospitalization over wave 2 and 3 compared to wave 1. Shown is a significant reduction of hospitalizations in wave 2 and 3. AUC = 0.7

DISCUSSION

This is the first study to assess severe outcome due to COVID-19 in patients with SSc over several waves. We demonstrated that patients with SSc showed a less severe disease course when infected with SARS-CoV-2 after the first wave with fewer instances of severe outcomes and hospitalization. A significant change in treatment patterns including immunosuppression for SSc and medical treatment for COVID-19 was observed. We show that severe outcomes decreased significantly after the first wave and stabilized in patients with SSc, not only because there were significantly fewer patients in need of ventilatory support, but even more importantly, because fewer patients were dying. This tremendous change occurred even before vaccinations were established broadly.

Previously it was shown that the disease course of the general population contracting COVID-19 improved across the waves, including patients with SARD.[6–8] Jorge et al showed reduced rates of hospitalization, deaths, ICU admission, mechanical ventilation, kidney replacement therapy, and acute kidney injury in their comparative cohort study of patients with SARD after the first wave in each of the following three-month periods of the pandemic.[7] Kawano et al recently verified these findings up to the Omicron era,[8] and like our results, they observed a decrease of patient's age over time. Patients with SSc were included in this study; however, they constituted only 2.4% of the population and were not investigated separately. In these studies, a better outcome of patients with SARD was noted over time and similar compared to the general population, as stated in the EULAR recommendation update from November 2021.[7,20,23] Importantly, the recommendation stated that "patients with some rare and severe systemic autoimmune or autoinflammatory diseases" cannot be included in this generalized statement, because of a more severe disease pattern.

In contrast, Conway and colleagues reported higher susceptibility of infection with SARS-CoV-2, as well as increased mortality in COVID-19 of patients with rheumatic and musculoskeletal diseases compared to patients without.[24] General risk factors were demonstrated to contribute to mortality of COVID-19.[19] This meta-analysis did not, however, consider COVID-19-independent risk factors and COVID-19 waves.[24] Again, specific information on patients with SSc was not available.

Comparison of outcomes of unvaccinated patients with either rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis arthritis, systemic lupus erythematosus (SLE), or SSc was done in a Greek study over a 12-month period between March 2020 and February 2021.[15] Incidence rates for hospitalization due to COVID-19 were higher in patients with RA, SLE, and SSc, and the OR for COVID-19–associated death was greater in patients with RA and SSc when adjusted for age and sex. Taken together, conflicting and insufficient data regarding the outcome of patients with SARD over time are available to date, especially regarding rare diseases such as SSc.

We also studied changes of general and SSc-specific characteristics across the waves. We showed that the presence of certain comorbidities, like arterial hypertension and the presence of more than two comorbidities, as well as age, decreased over time, in line with the improved general outcome. However, the proportion of men known to be associated with worse outcome in COVID-19 overall increased across the waves.[17,25] Except for SSc-associated cardiac disease, which is often oligosymptomatic and therefore potentially underdiagnosed in patients with SSc,[26] SSc patient characteristics did not differ among the waves. In multivariable analyses, we again show that, over waves 2 and 3, severe outcome and hospitalization decreased significantly and that only SSc-associated cardiac disease was associated with severe outcome. Hence, we regard the better outcome of COVID-19 in patients with SSc after wave 1 is not only attributable to patient- and SSc-specific characteristics, but also to increasing awareness and better patient management. This was supported by our analysis of the medical management of patients with both SSc and COVID-19, which showed the implementation of continuously adapted treatment recommendations. Except for specific substances like RTX and high-dose corticosteroids, treatment with immunosuppression, if clinically indicated, was expected to result in better control of the primary disease and consequently less risk of an unfavorable course in case of infection with SARS-CoV-2.[14,18,19] Interestingly, it seemed that these recommendations were implemented in clinical practice before official European-wide guidelines were established, because the updated EULAR recommendations were first published in November 2021. In addition, any and multiple COVID-19 treatments, especially antimalarials and antibiotics, were less frequently used over time as no benefit was shown, reflecting the up-to-date patient care of people with SSc. We therefore reason that the adherence to current treatment guidelines with adapting or continuing immunosuppressive therapy and COVID-19 treatment contributed to the better outcome of patients with SSc.

Our study has some limitations. Even though multiple relevant factors were identified, a direct causative relationship could not be determined with this study design. Nonetheless, we believe that the mentioned changes regarding the patient management may be relevant, especially as differences in patient and SSc characteristics across the waves did not seem to explain the observed findings sufficiently. Furthermore, a possible reporting bias cannot be excluded. Severe COVID-19 infections may have been reported more frequently at the start of the pandemic, whereas over time, less symptomatic patients may have consulted their physician and were included in the registry, or the other way round. However, SSc profiles did not change over time, which makes this less likely. Additionally, with vaccination programs starting at the beginning of 2021, some patients infected with SARS-CoV-2 in the later waves might have benefitted.

Finally, the inclusion of patients with a presumed COVID-19 diagnosis can be criticized. However, all the registered patients had classical symptoms and, to some extent, contact with a confirmed COVID-19 case.

A considerable strength of our study is the multicenter trial set-up with many countries represented. Determination of the time frame of each wave per country ensured comparability, allowing the creation of a solid study group of patients with a rare disease. We looked at multiple possible interfering factors, like general characteristics and comorbidities, SSc features, as well as medical management including SSc and COVID-19 treatment, covering the most important internal and external parameters influencing the outcome. Comparing our data to earlier findings, consistency exists in multiple aspects, hence supporting our results being of true significance and contributing essential knowledge on a large group of patients with SSc and COVID-19 compared to the smaller populations of patients with SSc in previous studies.

Severe outcome, including mortality of COVID-19 in patients with SSc, decreased after the first wave and stabilized over the second and third waves. To some extent, this was possibly due to intrinsic patient and SSc characteristics such as cardiac disease, but for the most part we attribute the change to extrinsic factors with improved patient management, higher awareness, and adherence to evidence-based recommendations. Even better outcomes are to be expected in further waves, with new and milder mutations, broadly applied vaccinations, and improved therapies against COVID-19.

ACKNOWLEDGMENTS

Open access funding provided by Universitat Zurich.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Distler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Deibel, Carreira, Vonk, del Papa, Bečvář, Guillén-Del-Castillo, Campochiaro, Poormoghim, Liem, Lazzaroni, Giollo, Mekinian, de Vries-Bouwstra, De Santis, Balbir-Gurman, Mihai, De Luca, Moiseev, Zanatta, Foti, Rednic, Denton, Cutolo, Belloli, Airo, Garzanova, Moroncini, İnanç, Panopoulos, Tandaipan, Chatelus, Rosato, Kuwana, Yavuz, Alegre-Sancho, Smith, Szűcs, Henes, Rodríguez-Pintó, Atzeni, Spierings, Truchetet, Milchert, Brito de Araujo, Riemekasten, Bernardino, Martin, del Galdo, Vacca, Mendoza, Midtvedt, Murdaca, Santiago, Codullo, Cacciapaglia, Walker, Brunborg, Tirelli, Allanore, Furst, Matucci, Gabrielli, Distler, Hoffmann-Vold.

Analysis and interpretation of data. Deibel, Distler, Hoffmann-Vold.

REFERENCES

1. Hoffmann-Vold AM, Distler O, Bruni C, et al. Systemic sclerosis in the time of COVID-19 [review]. Lancet Rheumatol 2022;4:e566–e575.
2. World Health Organization. Weekly epidemiological update on COVID-19 - 30 November 2022 (Edition 120). November 30, 2022. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—30-november-2022
3. Conway Morris A, Tong A. Novel treatments and trials in COVID-19. COVID-19 Pandemic 2022;109–120.
4. Kolifarhood G, Aghaali M, Mozafar Saadati H, et al. Epidemiological and clinical aspects of COVID-19; a narrative review. Arch Acad Emerg Med 2020;8:e41.
5. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis. PLoS One 2021;16:e0247461.
6. Bechman K, Yates M, Mann K, et al. Inpatient COVID-19 mortality has reduced over time: results from an observational cohort. PLoS One 2022;17:e0261142.
7. Jorge A, D'Silva KM, Cohen A, et al. Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study. Lancet Rheumatol 2021;3:e131–e137.
8. Kawano Y, Patel NJ, Wang X, et al. Temporal trends in COVID-19 outcomes among patients with systemic autoimmune rheumatic diseases: from the first wave through the initial Omicron wave. Ann Rheum Dis 2022;81:1742–1749.
9. Denton CP, Khanna D. Systemic sclerosis. 2017;390:1685–1699.
10. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–1905.
11. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. Nat Rev Dis Primers 2015;1:15002.
12. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR scleroderma trials and research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–1815.
13. Hoffmann-Vold AM, Brunborg C, Tirelli F, et al. POS0054 the impact and outcome of COVID-19 on systemic sclerosis patients from the European scleroderma trial and research group (EUSTAR). Ann Rheum Dis 2021;80 Suppl 1:232–233.
14. Avouac J, Airo P, Carlier N, et al. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Ann Rheum Dis 2021;80:e37.
15. Bournia VK, Fragoulis GE, Mitrou P, et al. Different COVID-19 outcomes among systemic rheumatic diseases: a nation-wide cohort study. Rheumatology (Oxford) 2023;62:1047–1056.
16. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–436.
17. Shi C, Wang L, Ye J, et al. Predictors of mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. BMC Infect Dis 2021;21:663.
18. Kroon FPB, Najm A, Alunno A, et al. Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations. Ann Rheum Dis 2022;81:422–432.
19. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930–942.
20. Landewe RBM, Kroon FPB, Alunno A, et al. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. Ann Rheum Dis 2022;81:1628–1639.
21. Alunno A, Najm A, Mariette X, et al. Immunomodulatory therapies for the treatment of SARS-CoV-2 infection: an update of the systematic literature review to inform EULAR points to consider. RMD Open 2021;7:e001899.

22. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20:533–534.
23. Serling-Boyd N, D'Silva KM, Hsu TY, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis 2021;80:660–666.
24. Conway R, Grimshaw AA, Konig MF, et al. SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. Arthritis Rheumatol 2022;74:766–775.
25. Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: a comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. PLoS One 2020;15: e0243191.
26. Bruni C, Ross L. Cardiac involvement in systemic sclerosis: getting to the heart of the matter. Best Pract Res Clin Rheumatol 2021;35: 101668.