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Severity and mortality of COVID-19 in patients with systemic sclerosis: a Brazilian multicenter study

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ABSTRACT

Introduction: COVID-19 may be associated with greater severity and mortality in patients with systemic sclerosis (SSc). The present study aimed to evaluate the prevalence, severity and mortality of COVID-19 in a Brazilian cohort of SSc patients.
Methods: This multicenter, retrospective, observational study included 1,042 SSc patients followed in four centers of São Paulo between March 2020 and June 2021. Diagnosis of COVID-19 was established by proper positive RT-PCR testing or by highly suspicious infection. Patients were grouped into mild (outpatient setting treatment and no need for oxygen support) and moderate-to-severe (hospitalization and/or need for oxygen support) COVID-19.
Results: Of the 1,042 SSc patients, 118 patients were diagnosed with COVID-19. Interstitial lung disease (SSc-ILD) was present in 65.6% of the total cohort and in 46.3% of SSc patients with COVID-19. There were 78 (66.1%) cases of mild COVID-19, and 40 (33.9%) cases of moderate-to-severe disease, with 6 (5.1%) deaths. By univariate analysis, pulmonary arterial hypertension (OR 9.50, p=0.006), SSc-ILD (OR 3.90, p=0.007), FVC <80% (OR 2.90, p=0.01), cardiac involvement (OR 5.53, p=0.003), and use of rituximab (OR 3.92, p=0.039), but not age, gender, comorbidities or use of corticosteroids, were predictors of worse outcome for COVID-19. Using multivariate analysis, only SSc-ILD was significantly associated to a higher risk of moderate-to-severe COVID-19 (OR 2.73, 95% CI 1.12-6.69, p=0.02). Forty percent of the patients remained with symptoms after presenting COVID-19, predominantly dyspnea and/or cough (17%).
Conclusion: In this cohort of patients with SSc, those with SSc-ILD were highly impacted by COVID-19, with a higher risk of moderate-to-severe COVID-19 infection and death.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic declared on March 11, 2020, by the World Health Organization (WHO), caused by the new coronavirus, named Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), has led to 220 million confirmed cases and more than 4.5 million deaths around the globe [1]. The course of COVID-19 is highly heterogeneous and, although most individuals present mild symptoms, 10-15% may require hospitalization and oxygen supplementation, and 5% can present critical manifestations, including respiratory failure, and multiple organ dysfunction [2,3].

Patients with systemic autoimmune rheumatic diseases (ARDs) are considered at risk of more severe infection due to both the immune dysregulation that characterizes these diseases and/or the use of immunosuppressive therapy, but it is unclear if they are more susceptible to development of COVID-19 than the general population [4]. However, this population may have an increased risk of worse outcomes, including severe symptoms, hospitalization, and intensive care unit (ICU) admission, although studies have shown conflicting results [4–6].

In this scenario, special attention should be given to patients with systemic sclerosis (SSc), a rare heterogeneous autoimmune disease, with the highest mortality among ARDs [7]. In particular, SSc interstitial lung disease (SSc-ILD) is a frequent complication, affecting up to

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70% of patients during the disease course [7]. Therapeutic options for SSc-ILD include mainly immunosuppressive agents, such as cyclophosphamide, mycophenolate, tocilizumab and rituximab [8]. Considering that lung disease and immunosuppression have been associated to worse outcomes during SARS-CoV-2 infection [8], it is important to better understand the effects and outcomes of COVID-19 in patients with SSc. Nonetheless, little information has been reported on the clinical course of COVID-19 in SSc.

Brazil has become one of the countries with the highest number of SARS-CoV-2 infection and mortality [9,10]. In this real-life observational study, we aimed to identify risk factors associated with COVID-19 severity and death in a large Brazilian SSc cohort, and also to investigate its prevalence in this population.

Materials and methods

Study design

This was a multicenter, retrospective, observational study, that analyzed data from 1,042 patients followed in four SSc specialized centers in the state of São Paulo, Brazil, from March 2020 to June 2021. Inclusion criteria were age ≥18 years and an SSc diagnosis according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria [11]. Patients with incomplete data in medical records were excluded.

All SSc patients had their electronic medical records thoroughly reviewed by rheumatologists with expertise in SSc. The primary outcome was to assess severity and mortality of COVID-19 in SSc patients within 90 days of COVID-19 diagnosis and to identify predictive factors associated with disease severity. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (CAAE 49433521.1.1001.5505).

Data collection

Clinical and demographic characteristics obtained from medical records included age, sex, disease subtype (limited or diffuse cutaneous SSc), last available measurement of skin thickness using the modified Rodnan skin score (mRSS), disease duration (defined as the time between the first non-Raynaud's symptom and the last available evaluation), presence of comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease [COPD] and obesity, considered in individuals with body mass index ≥30 kg/m^2), presence of specific SSc autoantibodies (anticentromere [ACA], anti-topoisomerase I and anti-RNA polymerase III antibodies) and current immunosuppressive therapy.

Information regarding systemic manifestations was also collected. The presence of esophageal dysmotility was evaluated by barium esophagogram, esophageal manometry and/or endoscopy. Pulmonary evaluation included pulmonary function test (PFT), chest high resolution computed tomography (HRCT) and echocardiography performed during the last 12 months. SSc-ILD was defined by the presence of any radiologic evidence of interstitial abnormalities on HRCT and forced vital capacity (FVC) <80% in PFT. Pulmonary arterial hypertension (PAH), suspected when pulmonary systolic arterial pressure was ≥40 mmHg or tricuspid regurgitation velocity was ≥2.8 m/s on echocardiography, was confirmed by right heart catheterization and defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg with a pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance >3 Wood units [13]. Cardiac involvement included arrhythmias, myocardial dysfunction and/or myocardiosclerosis documented by an electrocardiogram, echocardiogram or cardiac magnetic resonance imaging. History or presence of active digital ulcers (DU), scleroderma renal crisis (SRC) and musculoskeletal involvement (arthritis or myositis) was also registered.

COVID-19 was considered if the patient had SARS-CoV-2 infection confirmed by a positive reverse transcriptase polymerase reaction test (RT-PCR) or highly suspected infection. Highly suspected SARS-CoV-2 infection was defined as the 'presence of fever (axillar temperature >99° F) and/or known contact with a COVID-19 infected individual, plus four or more symptoms, such as dry cough, sore throat, shortness of breath, dyspnea, sudden worsening of preexisting respiratory symptoms, anosmia, dysgeusia, nausea, vomiting, headache and diarrhea', in accordance with the definition provided by Ferri et al [12].

COVID-19 was reported by the patients in regular medical appointments (either face-to-face or by telemedicine) and confirmed reviewing medical records. Data collected included clinical symptoms of COVID-19, oxygen support (non-invasive or invasive ventilation) and treatment setting (outpatient, hospitalization or intensive care unit requirement). Patients with mild COVID-19 and moderate-to-severe COVID-19 were compared. Mild COVID-19 was considered in patients with no need for hospitalization or oxygen support, while moderate-to-severe COVID cases were grouped together considering patients that required hospitalization and any kind of oxygen supplementation [14]. Status after SARS-CoV-2 infection was divided into recovery or death. Patients in the recovery group were investigated for presence of post-COVID syndrome, defined according to the National Institute for Health and Care Excellence (NICE) [15], when signs and symptoms developed after an infection consistent with COVID-19 continued for more than 04 weeks and were not explained by possible alternative diagnosis.

Statistical analysis

Statistical analysis was conducted with the IBM Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, IL, USA). After applying the Kolmogorov-Smirnov test to evaluate the normality distribution, continuous variables were analyzed using Student's *t*-test or the Mann-Whitney test and categorical variables were analyzed using the chi-squared test. Univariate and multivariate analyses were assessed and odds ratios with 95% confidence intervals were calculated using logistic regression. *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 1,042 patients (87.6% female, mean age of 53.8 ± 12.8 years) were followed in the four SSc specialized centers. Of them, 33.5% had diffuse cutaneous SSc and 65.6% had SSc-ILD (Supplemental table 1). During the study period, 118 SSc patients with COVID-19 were identified. The overall prevalence of COVID-19 in SSc patients was similar to that reported in the general population at the same time period (11.3% versus 10.3%, data from the São Paulo's State Secretary of Health) (table 1) [16–18].

Clinical features of the SSc patients who had COVID-19 are shown in table 2. COVID-19 diagnosis was confirmed by a RT-PCR test in 102 (86.4%) of the patients. SSc patients had a mean age of 51.0 ± 11.8 years, were mainly females (90.7%), with mean disease duration

Table 1
Estimated prevalence of COVID-19 in the general population of São Paulo and in the SSc cohort.

	SSc cohort	General population in the geographic area of São Paulo	*P*
Number of COVID-19 cases	118	1,490,636	–
Number of individuals	1,042	14,339,825	–
Prevalence	11.3%	10.3%	0.343

Table 2
Demographic and clinical features of SSc patients with COVID-19.

Variable	Whole cohort(n = 118)	Mild COVID-19(n=78)	Moderate-to-Severe COVID-19(n = 40)	*P*
Female/Male, n (%)	107 (90.7) / 11 (9.3)	73 (93.6) /5 (6.4)	34 (85) / 6 (15)	0.18
Age, mean ± SD	51.0 ± 11.8	52.2 ± 11.6	48.6 ± 11.9	0.11
Limited SSc/Diffuse SSc, n (%)	70 (59.3) / 48 (40.7)	47 (60.3) / 31 (39.7)	23 (57.5) / 17 (42.5)	0.77
Disease duration, mean ± SD	10.2 ± 9.1	10.9 ± 9.2	8.7 ± 8.9	0.141
mRSS, mean ± SD	7.7 ± 7.1 (n=116)	7.9 ± 7.2 (n=76)	7.3 ± 6.9	0.735
History or presence of DU, n (%)	48 (40.7)	32 (41.0%)	16 (40)	0.91
FVC % of predict, mean ± SD	76.9 ± 19.1 (n=110)	81.7 ± 17.4 (n=71)	68 ± 19.0 (n=39)	<0.001
FVC < 80%, n (%)	57 (52.7) (n=110)	31 (43.7) (n=71)	27 (69.2) (n=39)	<0.001
SSc-ILD, n (%)	51 (46.3) (n=110)	26 (36.6) (n=71)	25 (64.1) (n=39)	0.006
PAH, n (%)	10 (8.5)	2 (2.6)	8 (20)	0.003
Esophageal dysmotility, n (%)	98 (83.1)	63 (80.8)	35 (87.5)	0.35
Cardiac involvement, n (%)	16 (13.6)	5 (6.4)	11 (27.5)	0.003
SRC, n (%)	3 (2.5)	1 (1.3)	2 (5)	0.26
Arthritis or myositis, n (%)	65 (55.1)	44 (56.4)	21 (52.5)	0.68
Anticentromere, n (%)	22 (18.6)	15 (19.2)	7 (17.5)	0.81
Anti-topoisomerase I, n (%)	31 (26.3)	18 (23.1)	13 (32.5)	0.27
Anti-RNA polymerase III, n (%)	4 (3.4)	3 (3.8)	1 (2.5)	0.70
Comorbidity, n (%)				
Hypertension	29 (24.6)	21 (26.9)	8 (20)	0.40
Diabetes	11 (9.3)	8 (10.3)	3 (7.5)	0.74
COPD	7 (5.9)	6 (7.7)	1 (2.5)	0.42
Obesity	11 (9.3)	8 (10.3)	3 (7.5)	0.74
Comorbidity ≥ 1	43 (36.4)	31 (39.7)	12 (30)	0.29
Treatment, n (%)				
Glucocorticoids	23 (23.7)	17 (21.8)	11 (27.5)	0.49
Cyclophosphamide	3 (2.5)	2 (2.6)	1 (2.5)	1.000
Mycophenolate	36 (30.5)	20 (25.6)	16 (40)	0.109
Azathioprine	15 (12.7)	8 (10.3)	7 (17.5)	0.26
Tocilizumab	2 (1.7)	1 (1.3)	1 (2.5)	1.000
Rituximab	11 (9.3)	4 (5.1)	7 (17.5)	0.043
Methotrexate	19 (16.1)	15 (19.2)	4 (10)	0.19
Previous stem cell transplantation	10 (8.5)	8 (10.3)	2 (5)	0.49

COPD: chronic obstructive pulmonary disease; DU: digital ulcers; FVC: forced vital capacity; mRSS: modified Rodnan skin score; PAH: Pulmonary arterial hypertension; SRC: scleroderma renal crisis.

of 10.2 ± 9.1 years. SSc-ILD was present in 51 (46.3%) patients. Hypertension was the most frequent (24.6%) comorbidity in the cohort, followed by diabetes and obesity (9.3% each). Most patients (73%) were under current use of immunosuppressive agents, mainly mycophenolate. Stem cell transplantation was performed in 10 patients, and the mean time between stem cell transplantation and COVID-19 infection was of 4.5 ± 2.7 years (range 1 – 9 years).

Of the 118 SSc patients, 78 (66.1%) had mild COVID-19 and 40 (33.9%) patients presented moderate-to-severe COVID-19. Patients with moderate-to-severe COVID-19 had a higher frequency of ILD (64.1%), PAH (20%), cardiac involvement (27.5%), and previous use of rituximab (17.5%), compared to those with mild COVID-19 (36.6%, 2.6%, 6.4%, and 5.1%, respectively). Frequencies of comorbidities were similar between patients with mild or severe-to-moderate COVID-19 (table 2). When only patients with infection confirmed by RT-PCR test were analyzed, those with moderate-to-severe COVID-19 had a higher frequency of SSc-ILD, PAH, cardiac involvement, and use of mycophenolate and rituximab (Supplemental table 2).

Table 3 presents the frequency of symptoms and outcomes according to COVID-19 severity in SSc patients. Eighteen, out of the 40 patients with moderate-to-severe disease, required ICU and 8 needed mechanic ventilation due to respiratory failure. Six (5.1%) patients died, all of them due to severe presentation of COVID-19. Forty percent of the patients remained with some symptom after it, predominantly dyspnea and/or cough (17%) and musculoskeletal pain (12.5%), with a mean follow-up time of post-COVID-19 symptoms of 164 ± 119.2 days. Clinical differences regarding COVID-19 infection between SSc patients with SARS-CoV-2 infection confirmed by a RT-PCR test and those with highly suspected symptoms but without a RT-PCR test confirmation are shown in Supplemental table 3.

Predictors for moderate-to-severe COVID-19, according to univariate analysis, were presence of SSc-ILD (OR 3.9, 95% CI 1.37 – 6.96, p = 0.007), PAH (OR 9.5, 95% CI 1.91 – 47.22, p = 0.006), FVC < 80% (OR 2.90, 95% CI 1.27 – 6.63, p = 0.011), cardiac involvement (OR 5.53, 95% CI 1.76 – 17.33, p = 0.003), and current use of rituximab (OR 3.92 (1.07 – 14.33, p = 0.039) (figure 1). Using multivariate logistic regression analysis, SSc-ILD was the only variable significantly associated with a higher risk of developing moderate-to-severe COVID-19 (OR 2.74, 95% CI 1.12 – 6.69, p = 0.027) (table 4).

Univariate and multivariate analysis of the patients with COVID-19 confirmed by RT-PCR test are shown in Supplemental table 4. In these patients, SSc-ILD remained the only variable significantly associated to moderate-to-severe COVID-19 (OR 2.99, 95% CI 1.09 – 8.18, p = 0.032).

Discussion

In this study, we evaluated the frequency and clinical outcomes of COVID-19 disease in a large group of patients with SSc. Although, the prevalence of COVID-19 in SSc patients did not differ from that found in general population, we found a high frequency of moderate-to-severe infection (33.9%) with need for hospitalization, oxygen support and/or ICU admission in these patients. Furthermore, the presence of ILD, a frequent complication in SSc, was significantly associated with worse outcome by multivariate analysis. Death related to COVID-19 was observed in 5.1% of the patients.

Few studies have evaluated the frequency of COVID-19 in ARDs, and the main concern has been to investigate whether this group of patients has an increased risk of worse outcomes [4,19]. So far, data about frequency of COVID-19 in ARDs has presented conflicting results: one meta-analysis reported a rate of SARS-Cov-2 infection

Table 3
Clinical presentation and outcomes of COVID-19 infection in SSc patients.

Variable	Whole cohort(n = 118)	Mild COVID-19(n = 78)	Moderate-to-severe COVID-19(n = 40)	*P*
Fever, n (%)	78 (66.7)	47 (60.3)	31 (79.5) (n=39)	0.038
Cough, n (%)	105 (89.7)	67 (85.9)	39 (97.4) (n=39)	0.059
Dyspnea, n (%)	59 (50.4)	29 (37.2)	30 (76.9) (n=39)	<0.001
Anosmia, n (%)	74 (63.2)	51 (65.4)	23 (59) (n=39)	0.49
Headache, n (%)	67 (57.3)	47 (60.3)	20 (51.3) (n=39)	0.35
Sore throat, n (%)	30 (25.6)	25 (32.1)	5 (12.8) (n=39)	0.025
Myalgia, n (%)	95 (81.2)	64 (82.1)	31 (79.5) (n=39)	0.73
Diarrhea, n (%)	44 (37.6)	28 (35.9)	16 (41) (n=39)	0.58
Vomiting, n (%)	11 (9.4)	9 (11.5)	2 (5.1) (n=39)	0.33
Thromboembolic events, n (%)	3 (2.6)	0 (0)	3 (7.7) (n=39)	0.035
RT-PCR positive for COVID-19, n (%)	102 (86.4)	66 (84.6)	36 (90)	0.419
Outpatient setting treatment, n (%)	78 (66.1)	78 (100)	0 (0)	<0.001
Hospitalization, n (%)	40 (33.9)	0 (0)	40 (100)	<0.001
Noninvasive oxygen support, n (%)	34 (28.8)	0 (0)	34 (85)	<0.001
Mechanic ventilation, n (%)	8 (6.8)	0 (0)	8 (29.1)	<0.001
Intensive care unit admission, n (%)	18 (15.2)	0 (0)	18 (45)	<0.001
Post-COVID-19 syndrome, n (%)	45 (40.2)	31 (39.7)	14 (41.2) (n = 34)	0.88
Death, n (%)	6 (5.1)	0 (0)	6 (15)	0.001

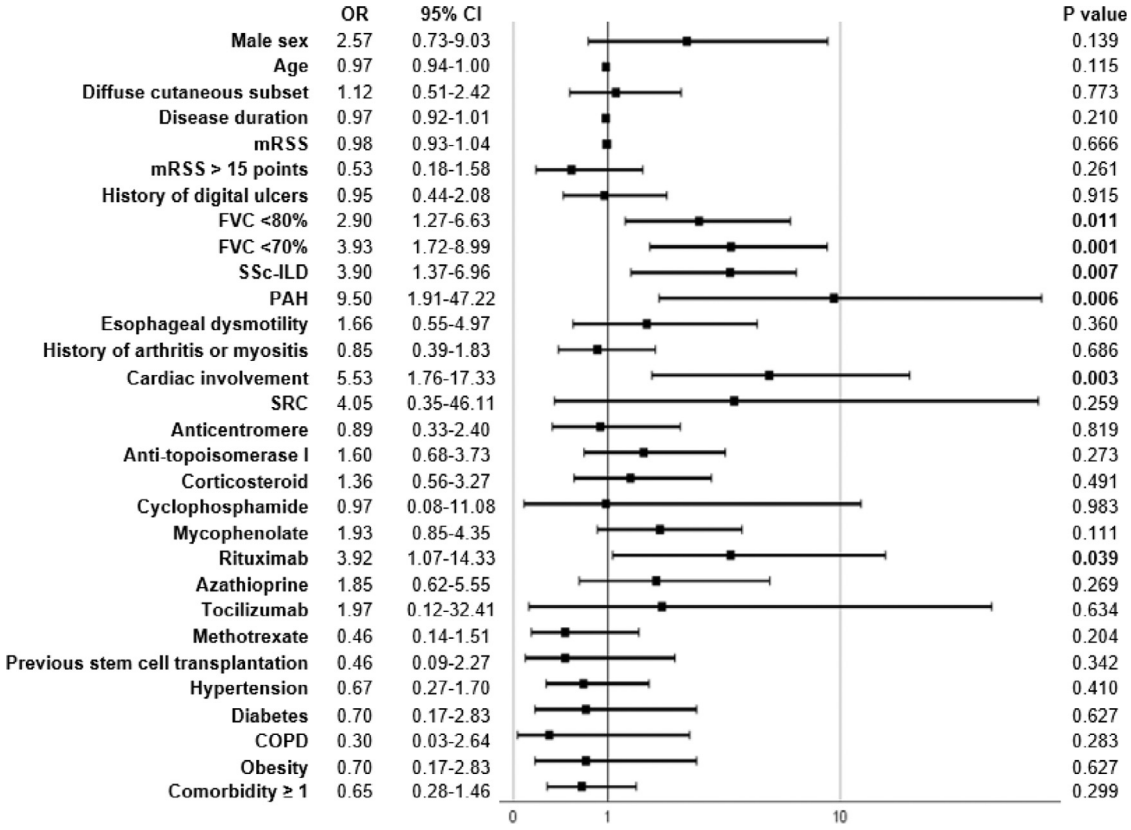

Figure 1. Forest Plot of risk factors for moderate-to-severe COVID-19 in SSc patients according to univariate analysis. COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; mRSS: modified Rodnan skin score; PAH: Pulmonary arterial hypertension; SRC: scleroderma renal crisis; SSc-ILD: systemic sclerosis-interstitial lung disease

similar to the general population, while other studies have shown a rate of infection one to three times higher than the rate of the general population [20–22]. We found an estimated frequency of COVID-19 in SSc patients similar to that for the general São Paulo's population, which is divergent from an Italian study that found a significatively higher prevalence of COVID-19 in SSc patients than the prevalence reported for the general Italian population [23].

Various studies have evaluated risk factors associated with severe forms of COVID-19 in the general population [3,11,24,25]. In most cohorts, older age [3,24], male sex, and the presence of comorbidities such as hypertension, diabetes, cardiovascular disease, chronic

Table 4
Predictors of moderate-to-severe COVID-19 in SSc patients according to multivariate analysis.

Variable	Multivariate analysis	
	OR (95% CI)	*P*
SSc-ILD	2.74 (1.12 – 6.69)	0.027
PAH	4.63 (0.69 – 30.91)	0.114
Cardiac involvement	2.57 (0.61 – 10.75)	0.193
Rituximab	1.91 (0.44 – 8.21)	0.384

PAH: Pulmonary arterial hypertension; SSc-ILD: systemic sclerosis-interstitial lung disease

pulmonary disease, chronic kidney disease, and malignancy are associated with hospitalization or worse prognosis [2,24,25].

In our study, one third of the patients had moderate-to-severe infection, requiring hospitalization or ICU admission. These findings are in line with prior studies that have assessed the frequency and severity of COVID-19 in patients with ARDs [5,26-29]. In the Global Rheumatology Alliance study, 46% of 600 cases of COVID-19 in patients with ARDs were hospitalized and 9% died [27]; while in the French cohort, the hospitalization rate was of 37% among 694 patients, with a mortality rate of 8.3% [5]. A recent United States (US) cohort study including 2,379 COVID-19 patients with ARDs found a higher risk of hospitalization, ICU admission, acute renal failure, and venous thromboembolism, albeit with no higher risk of death, when compared to patients without autoimmune rheumatic conditions [28]. These numbers are higher than those of the general population, as shown in the US cohort, in which 25% of the patients with ARDs were hospitalized compared to only 15% in the group of patients without ARDs [28], emphasizing the need for close monitoring of the outcomes of COVID-19 in ARDs' patients, including SSc.

Regarding mortality, we observed a mortality rate of 5.1%, which is in accordance with that of 4% observed in the US cohort [28], but slightly lower than the mortality rates observed in the Global Rheumatology Alliance study [27], in the French cohort [5], and in the Brazilian Registry of Rheumatic Patients with COVID-19, that reported a mortality rate of 9.2% among 130 patients with different ARDs [30]. Nonetheless, our study included only patients with SSc, while the percentage of SSc patients included in the aforementioned studies was very small (less than 4% of studied population). Hence, it is important to highlight that ARDs are a heterogeneous disease group, with varied clinical presentations and pharmacological management approaches, and different study designs do not allow direct comparisons. Thus, further studies are necessary to better assess the real mortality risk of COVID-19 in patients with ARDs, especially SSc.

Previous studies have shown a higher risk of worse COVID-19 outcomes in patients with pulmonary disease, including ILD [25,31,32], and Ferri et al [29] had already demonstrated a higher prevalence of COVID-19 in patients with ARDs and pre-existing ILD compared to those without lung involvement. In our study, the presence of ILD was significantly associated with moderate-to-severe outcome by multivariate analysis, highlighting the major impact of this manifestation in SSc patients with COVID-19.

Interestingly, unlike previous studies in patients with ARDs [33–35], we did not find an association with epidemiological data including male sex, age, and comorbidities, such as hypertension, and a higher risk of hospitalization or worse outcome in our cohort of SSc patients. We also did not find an association of corticosteroid or immunosuppressor use, such as cyclophosphamide and mycophenolate, with a higher risk of moderate-to-severe COVID-19. Although preliminary studies did not find an increased risk of severe COVID-19 in patients with ARDs using biologics and synthetic DMARDs [23,27,28], in our cohort the use of rituximab was associated with a higher risk of moderate-to-severe COVID-19 in the univariate analysis. Other reports have associated rituximab or IL-6 inhibitors use with severe outcome in patients with SARS-CoV-2 infection [36,37]. Avouac et al [36] reported need for hospitalization due to severe pulmonary involvement by COVID-19 in three patients with SSc that had been treated with rituximab. Despite of the low number of patients using rituximab in our study, we cannot exclude that B-cell depletion might be associated with severe outcome.

Of interest, 10 of the included patients had undergone previous stem cell transplantation (SCT) for severe SSc, as one of the centers that participated in this study is a referral center for the procedure in our country [38]. Considering that patients submitted to SCT are regarded as immunosuppressed or having significant organ dysfunction [39], they pose as a group vulnerable to worse outcomes after viral infections. Intriguingly, we did not observe worse outcome in this subgroup, probably due to the small number of transplanted patients, the long time since SCT was performed or, perhaps, more vigilant health care.

Even though most patients in our cohort recovered from the infection, approximately 40% remained with some symptom after it, predominantly dyspnea and/or cough and musculoskeletal pain. Our findings are similar to those described in other cohorts, where the prevalence of post-COVID syndrome varied from 32.6% [6] to 76% [40], with fatigue and dyspnea being the most commonly reported symptoms [41]. However, it is often difficult to differentiate manifestations that are secondary to the viral infection from those that are inherent to the baseline disease. Also, it is challenging to determine how much of the previous organ involvement by SSc delays the recovery from COVID-19, so the diagnosis of post-COVID syndrome must be interpreted with care. More studies are needed to better understand pathogenic mechanisms and possible treatments for persistent COVID symptoms.

Our study has several limitations including the retrospective design and small number of important events, such as death, that did not allow specific analyses. There was also a small prevalence of severe SSc manifestations, for instance PAH and cardiac involvement, and a low number of patients using immunosuppressors like cyclophosphamide, tocilizumab and rituximab, which may have an impact on our analysis. In addition, all four participating centers are located in the state of São Paulo, therefore the results here described may not reflect national outcomes for SSc patients after presenting COVID-19.

As vaccination is moving forward, the pandemic seems to be decreasing [42]. Nonetheless, challenges continue to emerge, including the appearance of new SARS-CoV-2 variants, COVID-19 sequelae, the global emotional distress caused by the pandemic, and the disparities on vaccination coverage among the world population [42–44]. Furthermore, the lower efficacy of COVID-19 vaccines in patients under some immunosuppressors, including those with ARDs, is of concern [45–47]. Therefore, it is important to be aware of specific populations with a higher risk for worse outcome, in order to implement specific health policies to better manage these individuals.

Conclusion

In summary, SSc patients, especially those with SSc-ILD and FVC < 80%, were more susceptible to severe clinical manifestation, with a higher risk of worse outcomes when affected by COVID-19. Therefore, they need to be carefully investigated and properly vaccinated against this dreadful new virus infection.

Authors contributions

All authors provided final approval of the manuscript and revised it critically.

S.M.O., L.V.O.M., M.C.O., P.D.S-B, and C.K., contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting of the article. A.P.L-A, A.C.M-R, acquired the data and contributed to the analysis and interpretation of data. D.A.M., A.P.T.D-R., acquired the data analysis and contributed to the interpretation of data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.151987.

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