Impact of COVID-19 outbreak in an Italian cohort of patients with systemic sclerosis

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Abstract

Background: Mortality rate in patients infected by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can be related to the presence of comorbidities like diabetes, cardiovascular and pulmonary diseases. On the contrary, few data exist on the impact of CoronaVirus Disease 2019 (COVID-19) on patients with rheumatic disorders, namely in those having pulmonary involvement and treated with immunosuppressive agents. The present survey is aimed at knowing the impact of COVID-19 in a cohort of patients with systemic sclerosis (SSc).

Methods: Telephone interviews were carried out during the COVID-19 outbreak in patients with SSc followed in a Rheumatic Disease Unit in Italy. Patients were asked for confirmed SARS-CoV-2 infection, symptoms suggestive of COVID-19, and modification of their therapy.

Results: A total number of 526 patients with SSc were contacted and interviewed. Of them, 270 and 256 had limited cutaneous and diffuse cutaneous SSc, respectively. Interstitial lung disease (ILD) was present in 45% of patients and most of them (68.2%) were treated with immunosuppressive therapy. Only two patients were hospitalized for COVID-19-related pneumonia, and one of them died despite invasive ventilator support. An additional 11 patients reported flu-like symptoms compatible with a mild form of COVID-19. Nobody modified the therapy during the COVID-19 outbreak.

Conclusion: Despite the large prevalence of ILD and immunosuppressive therapies, which can be considered risk factors for the occurrence and severity of incidental viral infections, the impact of COVID-19, in terms of mortality rate and morbidity, does not appear particularly severe in this large cohort of patients with SSc. Possible mechanisms influencing this figure are discussed.

Keywords: coronavirus, interstitial lung disease, mortality, outbreak, SARS 2, systemic sclerosis, viral infection

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Introduction

In December 2019 in the Hubei province of China began a pandemic outbreak sustained by a novel coronavirus named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The syndrome sustained by this virus was named CoronaVirus Disease 2019 (COVID-19), severe interstitial pneumonia being one of its most severe clinical features.[1] From its onset, the virus rapidly spread in the world, leading the World Health Organization (WHO) to declare a pandemic state. Since the first non-imported case of Italian infection reported in Lombardy on 21 February 2020, SARS-CoV-2 had a rapid spread mainly involving the Italian province of Lombardy and Veneto, in 1 month causing more deaths than China in triple the time.[2] To date, COVID-19 has shown a lower mortality compared with the most important other human coronavirus syndromes (Severe Acute Respiratory Syndrome-1 [SARS-1]; Middle East

Respiratory Syndrome [MERS]), but a dramatically greater spread.[1,3] This diffusion is favored by infective carriers in which the virus produces no or a mild flu-like syndrome during the whole duration of the disease or the incubation time (1–14 days). However, moderate to severe COVID-19 patients are very numerous and raise management concerns due to the saturation of Intensive Care Units. Great importance in the mortality associated with coronaviruses infection was given to the concomitant comorbidities of the patients. For COVID-19, a close correlation was found with diabetes, hypertension, cardiovascular disease, and to a lesser extent chronic obstructive lung disease, chronic liver disease and malignancies.[4] Immunocompromised patients are also rarely reported in SARS-1 and MERS cohorts and mainly referred to patients with active cancer.[5,6] The prevalence and impact of coronavirus infection in patients with rheumatic diseases are presently unknown. This may raise several concerns regarding the utility to continue immunosuppressive agents in this cohort of patients during the outbreak. This issue could be important in the management of systemic sclerosis (SSc) patients in whom different immunosuppressive agents are often prescribed. SSc is a connective tissue disease characterized by a complex pathological process in which the main scenario is represented by progressive loss of the micro-vascular bed, with the consequent progressive fibrotic changes in involved organ and tissues.[7] The most common cause of morbidity and mortality in SSc is pulmonary involvement.[7,8] Usually, this is in the form of interstitial lung disease (ILD) usually evolving to pulmonary fibrosis, affecting up to two-thirds of patients with diffuse SSc and a third of limited SSc patients.[9] These patients are commonly under immunosuppressive treatment with steroids, cyclophosphamide or mycophenolate mofetil (MMF).[8,9] Hypothetically, the presence of such a pulmonary comorbidity and the associated therapies could be factors for a more severe impact of viral infections often involving the lung is in this kind of population.

The aim of this report is to describe the prevalence and severity of COVID-19 in a large cohort of SSc patients during the epidemic of SARS-COV-2 in an area of high prevalence of the infection in Italy.

Methods

This observational study includes all SSc patients regularly followed in our tertiary referral centre at Gaetano Pini Hospital, Milan, Italy, from 8 March to 21 April 2020. All the patients had a diagnosis of SSc according to the latest version of SSc classification criteria.[10] The rapid increase of COVID-19 cases in Italy, with the main focus in Lombardy, has led the Italian government to start the lockdown on 8 March, greatly limiting all public activities and recommending staying home to all people. The Italian government, during lockdown, suggested performing only urgent outpatient visits, encouraging telephonic management for stable patients. In this view, all our patients were contacted by phone with a 2-week follow-up contact, in order to acquire data from possible SARS-CoV-2 infection. A specific questionnaire was prepared aimed at investigating the presence in each patient of symptoms consistent with COVID-19 (fever, sore throat, dry cough, diarrhoea, myalgia, hyposmia, ageusia). Demographic and previous clinical and serological data from each patient included in this survey, updated at the last clinical observation in our outpatient clinics, were withdrawn from our database.

Four investigators (NDP, AM, WM, FP) made the telephone calls using the questionnaire for patient interviews. The data collected during the interviews constituted the basis of the present survey and were also reported in the patient database. In the presence of complaints suggestive of COVID-19, patients were also asked whether they are or had been hospitalized, and had previous contacts with people with suspected or confirmed COVID-19. Specific questions were also included aimed at knowing whether the patients had varied the SSc-related treatment during the past few weeks. All the patients were also recommended to not modify their therapy in the following time.

In the case of breathlessness, swoon and/or fall of oxygen saturation under 92% at rest, patients were invited to follow national guidelines and then to call on the hospital emergency room to receive assistance for possibly more severe COVID-19.[11]

Patients described in this survey are also included in EUSTAR-COVID-19 database.

Results

A total of 526 patients with SSc are currently followed at the Scleroderma Clinic of our hospital. They include 380 patients from the north of Italy, 36 from central Italy and 110 from the south and islands. Demographics and SSc clinical

Table 1. Demographic and clinical characteristics of the patient cohort.

	Number	Percentage
Numbers of patients	526	
Median age, years (range)	59 (18–84)	
Median disease duration, years (range)	6 (1–25)	
Male/female	52/474	10/90
lcSSc/dcSSc	270/256	51.4/48.6
Autoantibodies		
ACA	255	48.5
Anti-Scl-70	242	46
Others (ANA, anti-SSA, anti-RNA pol III)	29	5.5
Interstitial lung disease	237	45
Mild	135	25.7
Moderate	60	11.4
Severe	42	8
Rheumatological treatment	359	68.2
Low dose glucocorticoids	234	44.5
Methotrexate	160	30.5
Mycophenolate mofetil	182	34.6
Rituximab	59	10
Tocilizumab	5	0.9
IVIG	2	0.4
Vascular therapies	474	90
Calcium channel blockers	167	31.8
Acetylsalicylic acid	302	57.4
ERAs	159	30.2
Phosphodiesterase inhibitors	30	5.7
Prostanoids	50	9.5

ACA, anti-centromere antibody; ANA, antinuclear antibodies; anti-RNA pol III, anti-RNA polymerase III antibodies; anti-SSA, anti-Sjögren's syndrome-related antigen A; dcSSc, diffuse cutaneous systemic sclerosis; ERAs, endotelin receptor antagonists; IVIG, intravenous immunoglobulin treatment; lcSSc, limited cutaneous systemic sclerosis.

characteristics are presented in Table 1. Our study cohort included 270 patients classified as being affected by limited SSc (lcSSc) and 256 diffuse SSc (dcSSc) on the basis of LeRoy's criteria.[12] A total of 359 patients (68.2%) were receiving at least one of these agents. As shown in Table 1, MMF was the most frequently administered agent (50.7% of patients), followed by methotrexate (44.5%), rituximab (RTX, 16.4%), while tocilizumab and IVIG were only occasionally

Table 2. Clinical characteristics of SSc patients with confirmed or suspected COVID-19.

	Confirmed COVID-19	Highly suggestive of COVID-19
Numbers of patients	2	11
Symptoms		
Fever	2	8
Cough	1	5
Sore throat	1	3
Rhinorrhea	0	1
Dyspnea	2	2
Myalgia	0	6
Arthralgia	0	6
Fatigue	2	5
Diarrhea	1	2
Nausea and/or vomiting	0	1
Anosmia/dysgeusia	2	7
Thrombosis	0	0
Chest X-ray pathological findings	2	1
CT chest pathological findings	2	Not performed
Hospital admission	2	0

CT, computed tomography; SSc, systemic sclerosis.

employed. Low doses of glucocorticoid (prednisone equivalent <10 mg) were also largely used (65.2% of patients). Regarding vascular therapies, around 30% of patients were receiving calcium-channel blockers, while 50.4% and 63.7% of patients were on treatment with advanced vasoactive agents (endothelin receptor antagonists, iloprost, and sildenafil), and with daily low-dose aspirin, respectively.

As shown in Table 2, in our cohort only two cases of COVID-19 infection were identified by rhinopharyngeal swab. Another 11 patients reported symptoms which were highly suggestive of COVID-19, but remained mild. In none of these 11 patients complaining of symptoms suggestive of COVID 19, was this suspicion confirmed by rhinopharyngeal swab or later by serological tests for specific antibodies. This was due to a national restriction concerning these tests, namely the swab test was reserved for patients admitted to the hospital for severity of their manifestation and to people who had close contacts with them. Serological tests were reserved for health service operators in COVID-19 dedicated units, or to people randomly selected from the general population for national epidemiological survey. Furthermore, 10 of these 11 patients did not undergo chest radiological assessment, because the national guidelines recommended that patients with a mild form of suspected COVID-19 had to stay at home until disease resolution to avoid overcharging hospital structures.

Among the two confirmed cases of COVID-19 infection, the first one, affected by dcSSc, had ILD classified as mild, according to a previously proposed staging system.[13] The patient was under treatment with weekly methotrexate and had received a rituximab two-infusion cycle 6 months before. The second patient, affected by lcSSc, suffered from pulmonary hypertension and was under treatment with combination therapy

(endothelin receptor antagonists and sildenafil). Both of them were hospitalized because of signs of respiratory failure and were treated with antibiotics, hydroxycloroquine and steroids. The first patient remained highly febrile under broad-spectrum antibiotics, the oxygen requirement increased progressively so that she finally underwent endotracheal intubation and mechanical ventilation for acute respiratory distress syndrome. Despite the additional compassionate use of tocilizumab, the patient died on 12 March.

The second patient rapidly recovered and, 3 weeks after, showed negative conversion of the rhinopharyngeal swab. Thus, the patient was discharged without any complications.

No one of the 13 patients with suspected or confirmed COVID-19 claimed clear previous contacts with people suffering from similar complaints before the lockdown time (8 March). This is not surprising as it has well known that SARS-COV-2 may have a long incubation period and may be present in many people without giving clinical manifestations. During the lockdown the risk of potentially infective contacts is obviously reduced in the survey population as well in the general population because of the adopted restriction rules.

Discussion

After entering Italy, COVID-19 has been spreading fast. As of 22 April 2020, the total number of cases reported by the authorities reached 187,000. The north of the country was mostly hit, and the region with the highest number of cases was Lombardy, which registered 74,000.[2] After more than 1 month from the SARS-CoV-2 outbreak in Italy, in our SSc cohort we report two cases of confirmed COVID-19 with severe complications requiring hospitalization, both of them coming from Lombardy. Only one of these two patients died as a consequence of SARS-CoV-2 infection. The mortality rate in our cohort, considering the cases resident in the north of Italy, could be estimated to be around 0.3%, while the prevalence of all symptomatic patients was 2.3%. The fact that strongly suspected COVID-19 in 11 patients was not confirmed by specific diagnostic testing may have induced a slight overestimation of this latter figure.

At the moment, it is not possible to compare the mortality rate and prevalence of COVID-19, either confirmed or highly suggestive in this SSc cohort with that of an age and sex-matched population

sample, as this last figure is still lacking even in Lombardy where SARS-CoV-2 diffusion is the highest. However, the prevalence of both confirmed and suspected COVID-19 in our patients with SSc suggests that this population is not particularly susceptible to this kind of infection, despite SSc patients taking different types of immunosuppressive therapy. This result is in agreement with the recent data derived from a physician-reported registry collected in a total of 600 patients with different rheumatic diseases by the COVID-19 Global Rheumatology Alliance.[14] In this survey an increased hospitalization rate was reported only in patients with glucocorticoid exposure ≥10 mg/day, but not in patients who took Disease Modifying Anti-Rheumatic Drugs (DMARDs) alone or in combination with biological agents. Unfortunately, patients with SSc represent only a minority in this cohort (3%). Notably, none of the SSc patients enrolled in this survey were taking a corticosteroid dosage ≥10 mg per day.

Severe COVID-19 pneumonia has recently been described in three patients routinely treated with rituximab to control different disease-associated manifestations, but not to contrast ILD that was not reported in these cases. In all these three patients a complete B cell depletion and a certain degree of hypogammaglobulinemia were present at the time of pneumonia occurrence. Despite these infection-favoring features all three patients had a favorable course of their pneumonia.[15] In this respect, the only patient in our series with a bad outcome suffered from an ILD and was treated with a single cycle of rituximab 6 months before. Immediately before the COVID-19 pneumonia occurrence the patient had neither lymphopenia nor a reduced level of gammaglobulins. So, it seems unlikely that previous treatment may have influenced the unfavorable course of COVID-19 in this patient. Conversely, one cannot exclude that the presence of ILD in this patient may constitute a negative prognostic factor.

ILD frequently complicates SSc, being present in up to 75% of patients, and represents the most frequent cause of SSc-associated death. Current treatment options aim at reducing pulmonary interstitial inflammation in order to counter the progression of fibrosis and consecutive deterioration of lung function. Current therapies of SSc patients focus on immunosuppressant agents, particularly cyclophosphamide and MMF.[8,9,16] More recently, consistent data have been published on the potential

effectiveness of rituximab and anti-interleukin 6 (IL6) receptor tocilizumab in the improvement/stabilization of SSc ILD.[17] Since the lung disease and immunosuppression are WHO-defined risk factors for a more severe course of COVID-19, SSc patients could represent a particular subgroup of patients at increased risk of respiratory or life-threatening complications from SARS-CoV-2 infection compared with other rheumatic diseases. This hypothesis is not confirmed by the present data collected in our large cohort of patients with SSc, although a large number of them were receiving immunosuppressive therapies. A recent case report from Mihai *et al.* on a patient who developed a mild form of COVID-19, even in the presence of ILD treated with tocilizumab and type 2 diabetes mellitus, appears to confirm our results.[18]

Different mechanisms can influence this unexpected not relevant prevalence and severity of COVID-19 in patients with SSc. Accumulating evidence suggests that patients with severe COVID-19 are characterized by acute systemic inflammatory response and cytokine storm, which can result in injury to multiple organs.[19] Disease severity and poor prognosis during SARS-CoV2 infection correlate with high circulatory levels of pro-inflammatory cytokines.[19] Furthermore, Xu *et al.*[20] found that an overactivation of T cells, namely the increase of Th17, and a high number cytotoxicity of CD8 T cells was present in the peripheral blood of a patient suffering from a severe and lethal form of COVID-19. The authors suggested that the important immune response could account for the severe lung immune injury in COVID-19 patients and that lymphopenia could be the result of lung sequestration of hyperactivated T cells.[21] As a consequence of that, the anti-inflammatory effects of immunosuppression could likely decrease the clinical expression of viral disease. Besides specific anti-IL6 effects mediated by tocilizumab, both cyclophosphamide and MMF act as regulators of proliferation, survival and maturation of T cells. Furthermore, MMF inhibits interleukin 17 (IL17) production with a specific inhibition of Th17 cells.[22] Thus, we can speculate that suppression of pro-inflammatory cytokines and T-cell activity by immunosuppressive agents might be protective, even in SSc patients. There is also some evidence that the use of anti-inflammatory agents, and namely of corticosteroids, may induce some improvement in the acute phase of this and other viral infections.[23]

Besides the protective role of anti-inflammatory and immunosuppressive therapies, we cannot rule out that the not relevant prevalence of COVID 19 in our cohort of SSc patients could be ascribed to other complex interactions between the host response to the viral infection and the physiopathological mechanisms of SSc. Host response to coronaviruses is mainly mediated by innate immunity. Type I interferon (IFN) represents one of the most important defense lines in virus infections.[24,25] Type I IFN stimulates the production of several proteins able to interfere with the virus replication and induce differentiation of antigen presenting cells able to interact with CD4+T cells leading to T helper and cytotoxic T lymphocyte response. IFNα and β (type I IFN) are able *in vitro* to interfere strongly with coronavirus replication.[26,27] Unfortunately, coronaviruses have peculiar mechanisms to escape to type I IFN as the replication in privileged sites and production of IFN antagonists.[28] IFNs also play a pivotal role in the pathogenesis of SSc as about 50% of SSc patients have an increased 'type I IFN signature' and treatment with IFNα could lead to a SSc exacerbation or trigger the disease onset.[29] Moreover, TLR3 and TLR4 [Toll-Like Receptors (TLR)] have been shown to be overexpressed in the skin and lungs of SSc patients, and both these receptors could have a protective role against coronavirus infections.[29–31] Thus, one could assume that the increased type I IFN signature and the overexpression of specific TLRs, pre-existing at the time of viral infection, might have a protective role in SSc against coronaviruses.

Macrophage involvement in viral infections is common. Macrophages at different activation status have different functional phenotypes. M1 macrophages are characterized as pro-inflammatory, tissue destructive, anti-tumoral, antimicrobial, and immunogenic. In contrast, M2 macrophages are anti-inflammatory, tissue repairing, pro-fibrotic, pro-tumoral, tolerogenic, and regulatory.[32] An excess in M1 polarization can produce severe inflammation and tissue damage, whereas an increase in M2 response can result in tissue fibrosis, allergy and risk of infections.[32,33] SARS-CoV-2 induces an excessive activation of M1 macrophages, causing viral spread through the lymphocytes and a massive death of macrophages through a cytokine storm.[34,35] In this view, the prevalence of M2 alveolar macrophages, namely in the lung context which is characteristic of patients with SSc, might have a protective role against SARS-CoV-2 infection, as already shown in lung pathology due to respiratory syncytial virus.[36] Usually, SSc patients show a

predominant M2 polarization, especially in the lung context.[37] This could be an additional reason for a low incidence of respiratory or life-threatening complications in our SSc cohort.

Another reason that may explain the not increased burden of COVID-19 in patients with SSc is that patients themselves, who are often well informed about their immune-compromised condition, have paid much more attention to the hygienic rules adopted to contrast the viral outbreak.

The present study has some limitations. First of all, most of our patients did not receive a nasopharyngeal swab. We do not know the real rate of SARS-COV-2 infected patients in our SSc cohort. However, the study was directed to evaluate only symptomatic patients, leaving the asymptomatic subjects out of the count. The telephonic approach could be another limitation of the survey, but it was chosen in accordance with the Italian government to minimize the numbers of patients in the outpatient clinic, avoiding further virus spread. Anyway, our Scleroderma Unit has been maintained open and then able to guarantee access to any SSc patient with unexpected complications including those potentially due to concomitant COVID-19. Finally, the outbreak is currently ongoing and possible new infections in our cohort cannot be excluded.

To our knowledge, this is the first report of the prevalence of coronavirus infection under the COVID-19 outbreak in a large SSc population. All our patients were advised to continue their current immunosuppressive regimen. These findings warrant further investigation, to confirm these preliminary data and allow improvement of the management of SSc patients during the COVID-19 outbreak.

Conflict of interest
The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate
The current analysis is part of a project to collect observational data from scleroderma patients followed at Gaetano Pini Hospital. The project was approved by the Ethics Committee with approval number 929/2019 bis. All included patients have signed an informed consent to participate in the data collection. The possibility of including this survey within the abovementioned data collection project has been waived by the same ethics committee, and verbal informed consent was obtained from all surveyed patients.

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