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COVID-19 and systemic sclerosis: clinicopathological implications from Italian nationwide survey study

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The ongoing COVID-19 pandemic caused by the novel β-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a serious challenge for the management of patients with different pre-existing comorbidities,[1–2] including rheumatic autoimmune systemic diseases.[3–5] These diseases affect a non-negligible proportion of individuals worldwide and are characterised by profound immune system alterations and increased susceptibility to infections, frequently aggravated by immune-modulating therapies.[3–6]

Among autoimmune systemic diseases, patients with connective tissue diseases or systemic vasculitis showed a higher prevalence of symptomatic SARS-CoV-2 infection (ie, COVID-19) than did patients with chronic arthritis.[4] Systemic sclerosis represents one of the most severe connective tissue diseases with multi-organ involvement due to concomitancy of fibrosing and microvascular alterations.[7] However, the literature on the impact of COVID-19 in patients with systemic sclerosis is limited to anecdotal reports or single-centre survey studies focusing on a miscellanea of rheumatic autoimmune disorders.[4,8,9]

See **Online** for appendix

Following the rapid spread of COVID-19 in Italy, the restrictions on individual movement have compromised the regular face-to-face activities of outpatient clinics; therefore, telemedicine has represented an effective alternative for the close monitoring of immunocompromised patients. Between March 15 and April 25, 2020, we carried out a nationwide survey study to investigate the cumulative prevalence of COVID-19 in Italian patients with systemic sclerosis resident in geographical macro-areas with different pandemic spread (high in north, medium in central, and low in south Italy). 1636 unselected patients with systemic sclerosis were consecutively investigated by means of a telephone survey done at 27 tertiary referral centres of 14 Italian regions (five northern, three central, and six southern) over a 6-week period. Clinical and serological assessment of patients with systemic sclerosis and telephone interview procedures, including a standardised symptom assessment questionnaire, were carried out as previously described.[4]

COVID-19 was classified according to currently used criteria as definite COVID-19 (signs or symptoms of COVID-19 confirmed by positive oral or nasopharyngeal swabs at PCR testing) or highly suspected COVID-19 (signs or symptoms highly suggestive of COVID-19, but not confirmed by PCR testing due to limited availability of virological tests in that period).[4]

The results of our nationwide survey are reported in the appendix (pp 1–2). Among 1636 patients with systemic sclerosis, mean age was 59·5 years (SD 12·8), mean disease duration was 11·2 years (8·7), female to male ratio was 8:1, 1112 (68%) patients had limited cutaneous systemic sclerosis, 278 (17%) had systemic sclerosis, 245 (15%) had sine scleroderma systemic sclerosis, 510 (31%) had symptomatic systemic sclerosis-related interstitial lung involvement, 425 (26%) had cardiomyopathy, 507 (31%) had serum anti-Scl70, and 736 (45%) had anticentromere

antibodies. Moreover, 1559 (95%) patients were taking at least one of the following drugs: low-dose steroids, conventional synthetic disease-modifying antirheumatic drugs, vasoactive drugs (often iloprost or other prostanoids, bosentan, or calcium channel blockers), or low-dose aspirin; biological disease-modifying antirheumatic drugs were administered in only 72 (4%) of 1636 individuals.

After the telephone survey, definite COVID-19 was reported in 14 (1%) patients and highly suspected COVID-19 in 47 (3%) patients (appendix p 1). These prevalences were invariably higher (p=0·0010) than the prevalence reported in the general Italian population of individuals with COVID-19 (349 per 100 000 population; data from the Italian Superior Institute of Health, updated report on April 28, 2020). Compared with the prevalence of COVID-19 in the Italian general population, the proportion of definite COVID-19 among patients with systemic sclerosis might be an underestimate, since 30% of COVID-19 cases in the Italian population in that period were asymptomatic; conversely, the prevalence of highly suspected COVID-19 among patients with systemic sclerosis might overestimate the prevalence of COVID-19 compared with the Italian general population.

The prevalence of COVID-19 in the macro-areas (Lombardy, Piemonte, Veneto, Emilia Romagna, and Liguria) of northern Italy was higher than that observed in the southern macro-areas (Campania, Molise, Puglia, Calabria, and Sicily; p=0·0030); moreover, significantly increased prevalence of COVID-19 was also found in patients with systemic sclerosis resident in Lombardy, the Italian region with the highest number of cases of COVID-19 in the general population (appendix p 1).

Clinically mild-to-moderate COVID-19 manifestations were observed in the majority of systemic sclerosis patients, whereas nine (15%) of 61 symptomatic individuals required hospital admission due to respiratory symptoms. Unfortunately, four of the nine patients who were admitted to hospital died: two men aged 81 years and 85 years, because of COVID-19-related severe pneumonia, and two women, a 42-year-old patient because of rapid worsening of pre-existing systemic sclerosis cardiopulmonary involvement, and 65-year-old individual with systemic sclerosis-related lung fibrosis complicated by acute respiratory distress syndrome, pulmonary venous and arterial thrombotic disease, and embolic stroke.

Definite COVID-19 was statistically more frequent in patients with pre-existing systemic sclerosis-related symptomatic interstitial lung involvement than in those without (p<0·0001; appendix p 2). Moreover, the presence or absence of COVID-19 did not correlate with other systemic sclerosis clinical or serological features; no associations were observed between ongoing treatments and the appearance of COVID-19 symptoms, with the exception of significantly lower prevalence of COVID-19 in patients treated with chronic low-dose aspirin than in those who were not (p=0·0060; appendix p 2).

Taken together, these findings are particularly noteworthy due to their pathological and clinical implications. Systemic sclerosis is the result of a multifactorial and multistep aetiopathogenetic process whereby numerous genetic, epigenetic, and environmental factors can affect the appearance of different clinical phenotypes and overall outcome.[7] Notably, COVID-19 and systemic sclerosis share pathological alterations: interstitial lung involvement that might evolve to fibrosis and endothelial injury responsible for diffuse microangiopathy.[7,10]

The fact that definite COVID-19 was more prevalent in patients with pre-existing systemic sclerosis-related symptomatic interstitial lung involvement (than in those without), together with the high prevalence of death among patients with systemic sclerosis admitted to hospital with COVID-19, suggests that the risk of severe COVID-19 is high in patients with systemic sclerosis.

These results, as well the low prevalence of COVID-19 in individuals undergoing chronic low-dose aspirin treatment, are in keeping with the pathogenic features described previously.[7,10] Besides the direct virus-related tissue damage, we hypothesise that SARS-CoV-2 might amplify the ongoing systemic sclerosis manifestations during the acute phase of viral infection; later, it might also contribute to advanced scleroderma organ damage. Long-term follow-up studies on large series of patients with systemic sclerosis and SARS-CoV-2 infection might clarify this issue. In-depth investigations on the possible interactions between SARS-CoV-2 infection and a compromised host immune system might provide useful pathogenic and therapeutic insights for both COVID-19 and systemic sclerosis.

Given the unpredictable, threatening course of the pandemic, valuable prevention and management strategies for particularly vulnerable individuals, such as patients with scleroderma, are highly advisable.

We declare no competing interests. We could not obtain written informed consent from our patients because of the telephone survey was done during the

For **Italian Superior Institute of Health data** see https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-national-surveillance-system

strict lockdown; therefore, all contacted patients who freely agreed to participate in the survey gave oral consent, according to the policy of our institutions.

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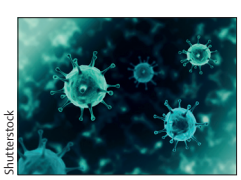
Divergent effects of acute versus chronic glucocorticoids in COVID-19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The COVID-19 pandemic has precipitated a search for both effective treatments and patient factors that predict poor outcome. Although agents ranging from convalescent plasma to Janus kinase (JAK) inhibitors have been trialled, to date the best evidenced acute therapy for severe COVID-19 is glucocorticoids. However, chronic glucocorticoid use has been found to increase the risk of poor outcomes in patients with COVID-19. This situation creates an interesting dichotomy.

Much of the pathology of severe acute COVID-19 is driven by the consequences of unconstrained activity of the host inflammatory response. Glucocorticoids have been found to be an effective treatment for COVID-19 in the acute setting, with 6 mg of dexamethasone (equivalent to 40 mg daily of prednisone) daily for up to 10 days reducing mortality from 25·7% to 22·9% (rate ratio [RR] 0·83, 95% CI 0·75–0·93).[1] These results were even more striking in patients who required oxygen (RR 0·82, 95% CI 0·72–0·94) or invasive ventilation (RR 0·64, 95% CI 0·51–0·81); notably those receiving no respiratory support did not benefit.

In contrast to the effect of acute glucocorticoids, registry data suggests that chronic glucocorticoids increase the odds of hospitalisation for COVID-19 in patients with