1. Title:

Demographic and clinical features of Portuguese Patients with Systemic Sclerosis: a Nationwide Multicenter Cohort Study

2. Background:

Systemic sclerosis (SSc) is a rare connective tissue disease of unknown etiology characterized by microvasculopathy, immune system disturbances and fibrosis of the skin and internal organs. The disease course varies from a relatively benign condition to a rapidly progressive disease, and has a wide spectrum of clinical and laboratory features.

Considerable ethnic and geographic variation in clinical and laboratory manifestations, severity and mortality has been observed in previous studies (1-3), suggesting the possible involvement of genetic and environmental factors. Therefore, investigating the distinctive manifestations and outcome of SSc patients in different ethnic and geographic groups is important, not only for a better understanding of this rare disease, but also to improve medical care. Although other cohorts have been published (4,5), large-scale national data do not yet exist.

The Rheumatic Diseases Portuguese Register (Reuma.pt) prospectively follows patients with several rheumatic diseases and in 2015 launched the registry of SSc patients. Reuma.pt gathers information on patient´s comorbidities, disease characteristics and the clinical evolution. As so, Reuma.pt is an excellent tool to evaluate Portuguese SSc patients.

Primary objetive:

- To investigate demographic and clinical features of Portuguese patients with SSc.

Secondary objetives:

- To examine overall survival rates of SSs and survival rates of limited cutaneous and diffuse cutaneous phenotypes
- To identify predictors of mortality in Portuguese SSc patients;
- To analyze treatment options in SSc;

Methodology

Prospective, multicenter, observational cohort-study of patients with diagnosis of SSc, using data from the Reuma.pt database.

Inclusion criteria: Patients with SSc diagnosis registered in the Reuma.pt database.

Variables:

• Demographic and clinical characteristics (gender, age, education, body mass index, lifestyle: ; smoking and alcohol consumption);

• Age of first symptoms;

• Age and calendar year of SSc diagnosis;

- SSc subtype (systemic sclerosis sin scleroderma; preclinic systemic sclerosis; limited cutaneous systemic sclerosis; diffuse cutaneous systemic sclerosis or overlap syndrome)
- Fulfillment of ACR 1980 or ACR/EULAR 2013 classification criteria

• Clinical SSc characteristics: Raynaud phenomenon, skin thickening, telangiectasias, digital ulcers, calcinosis, tendon friction rubs, arthralgia, arthritis, myositis and esophageal, gastric, intestinal, cardiac, pulmonary or renal involvement;

• Immunological characteristics: antinuclear antibodies (ANA), anti-Scl70, anti-centromere, anti-RNA pol III, anti-Th/To, anti-U3 RNP, anti-Pm/Scl, anti-Ku, Anti-U1 RNP, anti-U11/U12 RNP positivity

• Previous expositions that might cause skin thickening (silica, solvents, medications, etc)

- Comorbidities (hypertension, dyslipidemia, cardiovascular disease, diabetes, renal disease, osteoporosis, neoplasia)

• Treatment used: corticosteroids (CS), methotrexate and conventional synthetic DMARDs (csDMARDs); biological DMARD (bDMARD); vasodilators; proton-pump inhibitors

- Death
- Follow up time since diagnosis until death or last visit

Statistical analysis:

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and interquartile ranges for variables with skewed distribution. Descriptive analysis of categorical variables will be presented as frequencies and percentages.

5 and 10 years survival rates will be calculated. Kaplan–Meier analyze will be used to compare survival between limited cutaneous and diffuse cutaneous SSc.

Uni and multivariate models will be used to identify predictors of death

Follow-up time will be calculated as time in months from diagnosis until last observation or death

P- value will be considered significant at <0.05.

Expected results:

With this study we expect to characterize Portuguese SSc patoents.

Limitation of the study

Since registration in Reuma.pt database is voluntary, it is possible that some information is incomplete and some SSc patients are not introduce in the database. All participating centers will be invited to complete data whenever possible.

Calendar:

Data extraction: September 2020

Data analysis: November-December 2020

Final report: January 2021

Research team:

- Proponent: Raquel Freitas - Rheumatology department Hospital Garcia de Orta

- Research team: Fátima Godinho, Ana Cordeiro, Maria José Santos - Rheumatology department Hospital Garcia de Orta

- Institutions: The project is open to all National Rheumatology Centers interested in cooperating.

Co-authors: Authorship will follow the International Committee of Medical Journal Editors and Reuma.pt rules up to a maximum of 2 per center.

Ethical consideration:

The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and will be submitted for evaluation and approval to the Ethics Committee of Hospital Garcia de Orta.

Conflict of interest: There is no conflict of interest.

Funding: There is no funding

References:

1. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev 2010;9:A311-8.
2. Walker UA, Tyndall A, Czirjak L, Denton CP, Farge-Bancel D, Kowal-Bielecka O, et al; EUSTAR co-authors. Geographical variation of disease manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research (EUSTAR) group database. Ann Rheum Dis 2009;68:856-62.
3. Proudman SM, Huq M, Stevens W, Wilson ME, Sahhar J, Baron M, et al. What have multicentre registries across the world taught us about the disease features of systemic sclerosis? J Scleroderma Relat Disord 2017;2:169-82.
4. Ki Won Moon, Shin-Seok Lee, Yun Jong Lee, Jae-Bum Jun, Su-Jin Yoo, Ji Hyeon Ju, Sung Hae Chang, In Ah Choi, Tae Young Kang, Eun Bong Lee and Seung-Geun Lee. Clinical and Laboratory Characteristics and Mortality in Korean Patients with Systemic Sclerosis: A Nationwide Multicenter Retrospective Cohort Study. The Journal of Rheumatology. July 15 2018; doi:10.3899/jrheum.171443
5. Simeón-Aznar et al. Registry of the Spanish Network for Systemic Sclerosis. Medicine, volume 94, Number 43, October 2015